THE GEORGE BLUMER
EDITION OF
BILLINGS-FORCHHEIMER'S
THERAPEUSIS OF INTERNAL DISEASES

VOLUME III

THE GEORGE BLUMER
EDITION OF
BILLINGS-FORCHHEIMER'S

THERAPEUSIS OF INTERNAL DISEASES

CARE AND MANAGEMENT OF MALADIES
AND AILMENTS OTHER THAN SURGICAL

VOLUME III

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CHAPTER I

EPIDEMIC CEREBROSPINAL MENINGITIS

A. Sophian

INTRODUCTORY

The broad term "meningitis" indicates an inflammation of the meninges, the causes of which are many.

The causes may be divided into the bacterial and non-bacterial. The bacterial infective group produces a suppurative inflammation, and includes the following group of bacteria: the meningococcus, influenza bacillus, tubercle bacillus, Streptococcus pyogenes, Streptococcus mucosus capsulatus, pneumococcus, and staphylococcus; less commonly the typhoid bacillus, colon bacillus, the bacillus of bubonic plague, of glanders; the Bacillus pyocyaneus, the gonococcus, and Micrococcus tetragenus. In this group may properly be included poliomyelitis and its various subdivisions and syphilitic meningitis.

The non-bacterial division of meningitis includes a small group named "aseptic meningitis" and a larger group called "meningismus."

Aseptic meningitis is a suppurative meningitis not directly incited by any bacteria, but rather produced by a suppurative inflammation of tissues contiguous to the meninges; this most often refers to inflammation of the skull and its various sinuses, for example, complicating frontal sinusitis; in severe middle-ear infection, and infections of the cavernous and other skull sinuses.

The group classed as meningismus is of very common occurrence.

Meningismus is an inflammation of the meninges occurring during the course of general septicemic infections, resulting principally from the general toxemia which complicates and is part of the disease. It is most often seen in bronchopneumonia in young children, particularly in the form with extensive apical consolidation, and quite often in typhoid fever during the second and third weeks. The condition is essentially a toxic irritation of the meninges. No gross macroscopic changes can be found in the meninges postmortem, though some changes have been found in the membranes by careful microscopic examination. Vascular meningeal congestion and round cell infiltration are the outstanding microscopic features of this condition.

To summarize, meningitis is an inflammation of the meninges, which may be of infective origin, produced by any of the known pathogenic bacteria, or toxic irritative in origin, occurring during the courses of general bacterial infection, or complicating severe toxemia from any other cause.

The classification of meningitis may be further simplified by dividing the condition into primary and secondary meningitis.

Primary inflammation of the meninges may be produced by any of the following bacteria: the meningococcus, influenza bacillus, tubercle bacillus, and streptococcus mucosus capsulatus.

Primary meningitis caused by the tubercle bacillus very occasionally occurs, but infection undoubtedly is almost always secondary. We may, therefore, eliminate this germ from the classification.

Similarly, primary influenzal meningitis and streptococcus mucosus capsulatus meningitis, while occasionally seen, are practically unknown in epidemic form. These may also, therefore, be eliminated from important consideration in this group.

Meningococcic, or, as it is generally styled, epidemic meningitis, is the most important form of primary meningitis. It is the form which has caused large and repeated epidemics, and is most important from a therapeutic standpoint on account of its frequency and the high rate of mortality when not treated by specific measures.

Under the secondary form of meningitis may be grouped the other pyogenic forms of meningitis and meningismus. They all occur as a complication secondary to some other infection; thus streptococcic meningitis, as a rule, is secondary to streptococcic middle-ear infection; staphylococcic meningitis occurs secondary to general staphylococcic bacteriemia following some local staphylococcic infection either of the bones or infection of the soft parts. Meningismus, as has been explained, occurs secondary to some general systemic infection, usually one of the group of acute infectious diseases.

In encountering a case with symptoms of meningitis, therefore, the first and most important consideration is to determine with which form of meningitis one is dealing, and, if bacterial, whether it is due to the meningococcus or whether it is the secondary type of meningitis caused by some of the other bacteria cited.

The general clinical symptoms of all forms of meningitis are similar. A careful study of the history and onset of the disease, the grouping of symptoms, the diagnosis of some other primary infection as typhoid, pneumonia, middle-ear infection, or some other local infection, are undoubtedly of considerable importance in determining the type of meningitis from which the patient is suffering.

There is only one way to prove, however, whether a case of meningitis is infective or toxic in origin and to establish definitely the bacteriological type of the infection. An examination of the cerebrospinal fluid will, as a rule, clear up the diagnosis. It will furthermore materially aid the more accurate diagnosis of infantile paralysis and syphilitic meningitis, and will help to establish the diagnosis of toxic meningitis (meningismus).

During the course of an acute infectious disease, like pneumonia, it is sometimes very difficult, by clinical methods alone, to prove definitely whether complicating symptoms of meningitis are toxic and due to the original infection or whether the symptoms of meningitis are due to a coincident attack of pneumococcic, meningococcic, or other bacterial form of meningitis. Lumbar puncture with examination of the cerebrospinal fluid will readily differentiate the pathological condition.

It may be well in these pages to outline the laboratory findings in the cerebrospinal fluid in the various forms of meningitis, since upon this important step depends the application of the active curative, remedial measures.

TECHNIC OF EXAMINING CEREBROSPINAL FLUID

In examining the cerebrospinal fluid the following important data should be carefully noted: the pressure of the fluid as it flows from the needle, its color and turbidity, the presence of fibrin in the fluid, the cytology and bacteriology. In certain instances it will be necessary to make special serological tests and to inoculate animals with the fluid.

Pressure of Cerebrospinal Fluid.—Special instruments have been devised to determine the cerebrospinal fluid pressure, the principle in all being to measure the height to which the fluid will rise in a glass tube which is connected to the needle. Some use bent tubes; others, straight tubes; some, graduated; others, ungraduated. The height proper is ascertained by means of a tape measure. The bore of the tubing used by all approximates 1 mm. In terms of water pressure the normal cerebrospinal fluid pressure has been determined to be from 60 mm. to 130 mm. In a sitting posture the pressure is much higher.

It is unnecessary in most instances to take special measurements of the cerebrospinal fluid pressure. A normal cerebrospinal fluid flows from the needle very slowly, averaging about one drop every three to five seconds. In the various forms of meningitis, depending upon the amount of pressure and hydrocephalus, the fluid flows from the needle very much more forcibly, very often in a continuous stream. Thus, at a glance, one can readily determine whether one is dealing with a normal condition or with severe or moderate hydrocephalus.

The pressure of the cerebrospinal fluid in epidemic meningitis varies very considerably in different cases and at different stages of the disease. Early in the disease it is often only moderately increased, averaging not much over 150 to 300 mm. Late in the disease with the establishment of a chronic severe hydrocephalus in cases where there is free communication between the ventricles and subarachnoid space, the pressure is often very great, running up from 600 to 800 mm.

Careful observation of relative cerebrospinal fluid pressure at different lumbar punctures during treatment of a case of epidemic meningitis often gives an important clue as to the progress of the disease and the treatment that should be employed.

Color of Cerebrospinal Fluid.—A normal cerebrospinal fluid is clear and colorless. Tuberculous meningitis, except in rare instances, the various forms of syphilitic and parasyphilitic meningitis, poliomyelitis, and polioencephalitis yield a clear fluid containing fine flocculi. Epidemic meningitis and the other suppurative forms of meningitis yield a turbid fluid, the degree of turbidity usually depending upon the degree of infection.

Fibrin Content.—The microscopic fibrin formation can be readily determined in a normal fluid if, after removal, the fluid be permitted to remain undisturbed for a few hours. In most pathological fluids a fibrin network forms or clumps of fibrin settle upon standing.

Chemical Examination of Cerebrospinal Fluid.—A normal cerebrospinal fluid contains very little protein. In all inflammatory conditions of the subarachnoid space and ventricles, as a direct result of the inflammation, there is an increase in protein content in the cerebrospinal fluid.

The cerebrospinal fluid may be increased in quantity and pressure by causes other than infectious: (1) in tumor of the brain; (2) in cardiac and kidney incompetency with general anasarca; (3) in the meningismus form of irritation from any of the causes referred to; (4) in general convulsions in children from causes other than disease of the central nervous system; (5) in temporary hydrocephalus from severe headache and occasionally following the use of drugs. In these conditions, all of which may be accompanied by symptoms of headache, vomiting, vertigo, and other symptoms suggestive of meningitis and sometimes indicating a lumbar puncture, the cerebrospinal fluid examination for its chemical content will readily differentiate between the increase of the cerebrospinal fluid of non-infective origin and the true infective, inflammatory meningitis.

All of the tests described are concerned with the precipitation of protein by chemicals. A simple test is the layering of pure nitric acid over the cerebrospinal fluid, the appearance of a cloud at the junction indicating a positive reaction. A similar one consists of the addition of a few drops of 5 per cent acetic acid to a few cubic centimeters of fluid, likewise causing the appearance of a white precipitate when positive.

A somewhat more delicate test is the Nonné test. This is divided into two phases, the first being obtained by adding saturated ammonium sulphate solution to cerebrospinal fluid in equal parts. This precipitates the globulin. After three minutes an estimate should be made of the degree of reaction. All fluids, including the normal, yield a cloud in this phase. In the second phase the mixture is filtered, and to the filtrate is added one drop of dilute acetic acid, and the solution is boiled. The appearance of a cloud is believed to be due to a serum albumin of inflammatory origin, and is considered a positive reaction.

Another test of equal delicacy is Noguchi's globulin test. This is performed by mixing one part of cerebrospinal fluid with five parts of 10 per cent butyric acid in physiological salt solution, boiling, then quickly adding one part of a normal solution of NaOH and boiling again for a few seconds. A normal fluid produces a slight, white, diffuse cloud that does not precipitate. An exudate from inflammatory meningitis produces a heavy white cloud that precipitates in the form of large flocculi. Noguchi advises that a fluid should be allowed to stand from at least one-half to one hour before readings are made.

Another test, which in the writer's experience has not been of as great help as the others, described by Braun and Husler, consists of the addition of 1 c.c. of cerebrospinal fluid to n/300 HCl and slowly shaking. If clouding does not occur after 5 c.c. have been added the reaction is considered negative. Sometimes a positive reaction does not occur for one-half hour.

The gold chlorid test and other tests, all of which are concerned with the chemical precipitation of the albumins and globulin, have been used. The very simple acetic acid and the nitric acid tests are almost of as great significance as the more complicated tests recommended.

Another chemical means recommended for differentiating between inflammatory fluids, normal fluids, and transudates is the reduction of Fehling's solution by the cerebrospinal fluid. A normal fluid reduces Fehling's solution after the addition of a few cubic centimeters of fluid. Most observers believe that purulent fluids and fluids of tuberculous meningitis do not reduce Fehling's solution. It is true that gross reduction does not as readily occur in purulent fluids and fluids of tuberculous meningitis as in normal fluids, but upon adding a sufficiently large quantity of fluid in any inflammatory condition and boiling with Fehling's solution a reduction sediment can, in many instances, be determined if the fluid be allowed to settle for a few hours before examination. In the writer's experience this test is of little, if any, significance.

To recapitulate: It must be borne in mind that the chemical examination of the cerebrospinal fluid for reduction of Fehling's solution and the presence of protein content are not of definite diagnostic significance, being of value only in differentiating grossly normal fluids and transudates from the fluids in inflammatory meningitis, whatever the cause.

Bacteriology.—This is the most important examination of the cerebrospinal fluid and one that can easily be employed in the office of the general practitioner. The technic is as follows: Fluids should be centrifuged for several minutes until a moderate amount of sediment is collected. The supernatant fluid should be poured off and used for the chemical tests. A little of the sediment is smeared on a glass slide and stained with Gram's stain. If influenza meningitis be present the sediment should be stained with fuchsin, as sometimes the influenza bacilli may be missed with simple Gram stain. If bacterial, suppurative meningitis be present the causative bacteria can be readily demonstrated in moderate or large numbers in most instances. If tuberculous meningitis be suspected the fluid should be centrifuged for a longer period, from one-half to one hour, and the greater part of the sediment should be smeared over a cover slip and allowed to dry. A part of the fibrin network should be fished out and streaked over the same slide as the sediment. After drying the cover slip or slide should be stained with the regular Ziehl tubercle stain; tubercle bacilli, in the great majority of instances, will be found, though few in number, after a patient search.

In the usual pyogenic meningitis, after a loopful of sediment is taken from the smear, several loopfuls should be streaked on suitable culture media, the most favorable media being that containing the usual nutrient agar mixed with 1½ per cent glucose and ⅙ the volume ascitic fluid or sterile animal serum. After incubation for eighteen to twenty-four hours at 37° C. a growth usually appears, though sometimes in influenzal meningitis the growth is delayed for three to four days. Gram's stain of this growth and the morphological appearance of the growth will usually enable positive diagnosis at this time. Further cultural identification of the growth must, of course, be made when necessary. In meningococcus meningitis the findings are usually typical. The Gram-negative biscuit-shaped diplococci, extracellular and intracellular, the irregular staining of the cocci, their frequent clumping, the typical appearance of the colonies, the tendency to rapid autolysis of the germ in culture media and in salt solution permit of diagnosis within a very short time.

Cytology.—Careful cytological examination of the cerebrospinal fluid will yield considerable information of great diagnostic importance. The method consists in determining the total number of cells in the cerebrospinal fluid and in differentiating the type of cells. The simplest method employed is that in which the cerebrospinal fluid after its removal is centrifuged and the sediment poured on a slide as for the bacteriological examination; after staining, the number and type of cells as they appear in the smear are determined. A normal fluid shows an occasional endothelial cell or lymphocytes in the field. In all forms of inflammatory meningitis the cells are considerably increased in number. The type of cells depends upon the character of the inflammation. In purulent inflammation, due to the usual pyogenic bacteria, such as meningococcus, streptococcus, pneumococcus, and the others, the bacteria are almost wholly pus cells, polymorphonuclears. In tuberculous meningitis, syphilitic and parasyphilitic meningitis, poliomyelitis, and polioencephalitis the cells are usually lymphocytes.

More accurate methods for determining the number of cells have been devised and used. The principle in these methods is the actual counting of the cells on a blood-counting slide. Some workers centrifuge the fluid and study the sediment on a blood-counting slide, while others recommend the use of a staining fluid which should be mixed with the cerebrospinal fluid immediately after removal, and then the cells counted in the regular counting chamber as for a blood examination. The staining solution commonly used consists of the following.

Methyl violet	.1
Glacial acetic acid	2.0
Distilled water to make	50.0

This solution is drawn up into an ordinary white-blood-counting pipet to the .5 mark and the cerebrospinal fluid drawn up into the diluting chamber as for a regular blood count. Either a regular blood-counting chamber may be employed or special chambers which have been devised.

A normal cerebrospinal fluid contains on an average of seven to ten cells per cubic millimeter. In inflammatory meningitis the cells as mentioned are considerably increased up to several hundred cells per cubic millimeter.

The above-described examinations constitute the usual studies of the cerebrospinal fluid. In suspected tuberculous meningitis, even where the bacilli have been found in the cerebrospinal fluid, a few cubic centimeters should be injected into a guinea pig. If positive, the guinea pig will usually develop miliary tuberculosis in four to six weeks.

Serological studies of the cerebrospinal fluid are only of academic interest, but are not of immediate practical application.

In the premeningitic stage before the full establishment of the symptoms of meningitis the cerebrospinal fluid is increased in quantity, clear, sometimes showing a slight increase in fibrin and a faint increase in the total protein content as demonstrated by the chemical tests previously described. Cytology shows either no increase or a moderate increase in cells, the latter most often being lymphocytes. Sometimes these cells are equally divided between lymphocytes and polymorphonuclear cells; at other times polymorphonuclear cells predominate. As a rule, however, early in the premeningitic stage, lymphocytes are more numerous. As this stage merges into the true stage of meningitis polymorphonuclear cells are in excess, and in the true stage of meningitis polymorphonuclear cells practically exclude all other types of cells.

The stained sediment of the fluid in the premeningitic stage shows most often no bacteria or may exhibit a few free Gram-negative diplococci. These are evidence, and are part of the general bacteriemia rather than an indication of the localization of the organism in the meninges. Late in this stage of the disease the organisms are more numerous and free, and then indicate the beginning of the localization of the meningococci in the meninges. Culture early in this stage when the organisms are few is, as a rule, negative. Late in this stage it is usually positive, showing after eighteen to twenty-four hours' incubation the usual characteristic growth of meningococcus.

In the fully developed case of meningitis the cerebrospinal fluid usually shows the following classical findings: a turbid fluid from slightly opalescent to thick, viscid, plastic pus usually under high pressure and markedly increased in quantity; at times 100 c.c. or more fluid may be easily removed. Fibrin and protein content is very markedly increased. A study of the sediment demonstrates a very pronounced increase in cellular elements, practically all of the cells being polymorphonuclears. The stained smear usually exhibits varying numbers of Gram-negative diplococci, both extracellular and intracellular. In severe cases, before serum treatment, or in cases which are not responding to serum treatment, most of the bacteria are extracellular. With favorable response to serum treatment, or in cases that are doing well without serum treatment, the bacteria are fewer in number, most being intracellular. With favorable response there is often a tendency for the organisms to clump. The bacteria ordinarily stain very irregularly in smear, some taking a deep stain, others being mere shadows. There is often a tendency for the bacteria to diminish rapidly in numbers after the disease has lasted only a short time, even if there be no improvement in the clinical condition or if the disease be aggravated. In this instance, however, the bacteria, though few, are almost altogether extracellular.

In the chronic form of meningitis the cerebrospinal fluid findings vary, depending upon the type of infection. In the severe form of the disease the findings are exactly the same as in the usual acute form of epidemic meningitis except that the pus cells are less numerous and lymphocytes abound in larger proportion. The longer the case lasts the greater the tendency for the percentage of lymphocytes to increase and the percentage of polymorphonuclear cells to diminish. If serum treatment be instituted in these cases, even if there be no improvement, there is generally a prompt change in the cytological picture. Polymorphonuclear cells promptly increase, and may entirely replace the lymphocytes. In the mild form of the disease the fluid is usually only slightly opalescent and very markedly increased in quantity; fibrin and protein content is moderately increased; the number of cells is moderately augmented, the lymphocytes being equally divided with the polymorphonuclear leukocytes; the bacteria, often clumped and intracellular, are usually very few, very often a few also being extracellular. If serum treatment be introduced, and if there be response, the cells, mostly polymorphonuclears, increase considerably in number. With this the few extracellular bacteria become intracellular, and with further treatment the bacteria totally disappear.

TREATMENT OF EPIDEMIC MENINGITIS

The present recognized treatment of meningitis is one of the great scientific achievements of the twentieth century. It was brought about by a very careful study of a number of important factors: the bacteriology of the meningococcus; the recognition of the pathological sequence of the meningococcus infection, and the recognition of the fact that the meningococcus infection is first a violent bacterial infection, which begins as a severe, general meningococcic bacteriemia that only later is followed by an infection of the cerebrospinal meninges.

It was learned that sometimes a patient dies from the severe general bacteriemia even before the infection localizes in the meninges. With localization in the meninges the disease, to a very great extent, becomes a local one, the general sepsis, as a rule, abating or dying out.

The treatment after meningitis sets in resolves itself, as in other local infections, into combating and destroying the infectious agent and relieving the immediate urgent symptoms resulting from the local multiplication of the infectious agent. The treatment thus consists of specific serum therapy for the infection and the removal of the exudate caused by the infection. In all inflammations of the meninges this is most important on account of the hydrocephalic symptoms resulting from the confinement of the exudate in the meninges, which are bounded on one side by the bony skull and on the other side by the softer brain tissues. As the fluid collects in larger quantities pressure is thus exerted on the important centers within the brain.

The first advance in this field of study was the preparation of a specific immune serum. This was done almost coincidentally by Flexner in this country and Jochmann, Kolle and Wassermann abroad. All investigators worked practically along the same lines, and attempted to produce a serum of high opsonic, bactericidal, and antitoxic properties.

Similar methods were employed by all. At first smaller animals (the rabbit) were used; later larger animals were immunized—the goat, sheep, monkey (by Flexner), and finally the horse. The methods used and generally now accepted are as follows: injections of dissolved meningococci (so-called meningococcic extract) in increasing quantities, followed by injection of live culture in increasing quantities. The object of the former is to produce a serum of high antitoxic potency and the latter to produce a serum of high opsonic and bactericidal properties. Horses are now generally used. After two months a horse, as a rule, can endure large doses of this virulent material. After a period of injection, usually about four months, the serum of the horse is sufficiently potent to be used therapeutically. An index of high potency has been established—a high opsonic index; the ability to cause phagocytosis of meningococci in not less than 1:5,000 solution of the serum; the presence of bactericidal bodies and complement-fixation bodies; the presence of antitoxic bodies and the ability to protect smaller animals against fatal doses of culture.

To recapitulate: The specific infectious agent, the meningococcus, was found to be the cause of epidemic meningitis; next the mode of infection and the pathological sequence were learned, then an immune serum was produced which experimentally, at least, was proved by biological tests to be of high potency.

The last and most important step was to apply the serum in human beings in treatment of the disease. At first it was used like other sera and antitoxins. Varying doses were injected subcutaneously and intravenously. Varying and indifferent results were obtained. Flexner first proved by experimental tests in the monkey that the antimeningitis serum injected subdurally offered best results. The subsequent clinical use of the antimeningitis serum in this way helped to establish definitely the antimeningitis serum as a reliable therapeutic agent of tremendous possibilities.

It has been found that immune sera when injected into the general circulation either by subcutaneous injection or intravenous injection are eliminated into the cerebrospinal fluid in very minute quantities. On the other hand, the injection of immune sera into the subarachnoid's space is followed by very rapid elimination of the serum into the general circulation. It has been explained that epidemic meningitis once fully established is essentially a localized process, the accompanying general bacteriemia during this stage being much less important. We now see the reason for the early failure with the antimeningitis serum when injected subcutaneously and intravenously. In order to attain good results in epidemic meningitis with the specific antimeningitis serum the latter must be injected by lumbar puncture directly into the cerebrospinal subarachnoid space, where it is brought into close contact with the infected area.

It has not been proved whether or not serum injected by lumbar puncture into the subarachnoid space reaches the infected ventricles. Clinical observation certainly points to the early diffusion of such serum throughout the subarachnoid space into the ventricles. How otherwise explain the prompt clinical subsidence of symptoms, the declining of pressure phenomena, and prompt clearing up of the cerebrospinal fluid following the successful treatment with the antimeningitis serum? The little experimental work that has been done on this subject, however, does not corroborate this view. Graves, in 1912, in a series of observations on dogs, failed to demonstrate diffusion to the ventricles. Staining fluid injected by lumbar puncture could not be demonstrated in the ventricles after death. Likewise some staining fluid was added to the immune antimeningitis serum and injected therapeutically in a few cases. The staining material of course was innocuous. One patient died of the disease, and postmortem failed to demonstrate the staining material in the lining of the ventricles.

The last step in the elaboration of a specific, scientific treatment for this disease was the establishment of safe and correct methods of administering the antimeningitis serum. After learning that the antimeningitis serum acted locally by bathing the infected parts, it was of course thought desirable to inject as much of the specific serum as could be done safely. It was at first thought that after lumbar puncture was performed, and cerebrospinal fluid removed in any quantity, a serum equal in quantity to the cerebrospinal fluid removed could be safely injected. On this basis the dose of the antimeningitis serum was an arbitrary quantitative one, depending upon the quantity of the cerebrospinal fluid removed, believing that at least an equal quantity of fluid could be safely injected. This method in general was followed by fairly good results. The writer, however, in a careful study of a great many cases noticed occasionally attacks of collapse, respiratory embarrassment, convulsions, and even death, following the injection of the antimeningitis serum, the dose being determined as already explained. Believing that possibly the arbitrary method of determining the dose was unsafe, he undertook more careful study, and ultimately found, as he had at first suspected, that the arbitrary quantitative method of determining the dose was not only unsafe, but at times very dangerous and occasionally even resulted in death.

Observations on the cerebrospinal fluid pressure were first made. Readings at the beginning of puncture, during the removal of the cerebrospinal fluid and during the injection of the antimeningitis serum, were made. It was thought that if, after removal of the cerebrospinal fluid, the dose of serum were guided by the cerebrospinal fluid pressure, so that when the cerebrospinal fluid pressure became equal to that at the beginning of removal of cerebrospinal fluid, it should be considered that a full dose of serum had been administered, in this way the pressure conditions in the subarachnoid space would be reëstablished and the dangerous symptoms eliminated. It was found very early, however, that these observations were very misleading and dangerous and were absolutely no criterion as to the quantity of serum that could be safely injected.

Blood-pressure studies were then begun. The writer very soon came upon some very interesting data. He found first that the injection of the antimeningitis serum in quantity equivalent to the fluid removed did not reëstablish conditions. Removal of cerebrospinal fluid was usually accompanied by a moderate fall in blood-pressure. Quite often, however, no change in blood-pressure followed; other times the blood-pressure rose. Injection of antimeningitis serum, however, uniformly in the great majority of cases produced a fall in blood-pressure. The blood-pressure dropped and continued to drop as larger quantities of fluid were injected. The fall in blood-pressure likewise depended very largely on the rate and pressure used in the injection of the serum. There was absolutely no relationship between changes in blood-pressure following the removal of cerebrospinal fluid and the changes following the injection of the serum. If the injection of the serum were continued in spite of the warning fall in blood-pressure, symptoms of respiratory embarrassment, shock, convulsions, and even death ensued.

As a result of these findings the writer concluded: (1) that the arbitrary quantitative method of determining the dose of the antimeningitis serum was inaccurate and dangerous; and (2) that the blood-pressure changes noted during the injection of the antimeningitis serum offered a valuable guide as to the quantity of serum that could be safely injected.

Classical Method of Performing Lumbar Puncture and Administering Antimeningitis Serum

Anesthesia.—General anesthesia is dangerous, and should not be employed except where positively indicated in violent, delirious patients or in highly sensitive, nervous patients. Local anesthesia is worthless. The severest pain during lumbar puncture occurs when the spinal membranes are perforated. A quick puncture, skillfully performed, is very often a mild operation.

Site of Operation.—The site of operation should be sterilized and draped off as for a major operation. It is desirable to select a level for puncture below the conus medullaris. In this way danger of injuring the cord is eliminated and there is less likelihood of injuring the nerve roots. The level of the conus varies in different people. In young children it is very often slightly lower than in adults. The fourth lumbar space, which is at the level of the crest of the ilium, is below the level of the conus. This site, or the lumbosacral space, is, therefore, usually selected. After a number of punctures on different days it may be desirable to select another level. Adhesions may form and shut off the subarachnoid space at the operated level, and there may be danger of infection from the irritated and inflamed skin over the puncture. The next space above, the third lumbar space, should then be chosen and, if necessary, even the second or first lumbar space may be selected. Puncture at the latter two levels, however, is attended by greater danger of perforating the cord and consequently injuring some of the important nerve centers, notably those of the bladder, rectum, or roots of the lower extremities. This danger, however, is not so imminent, since in epidemic meningitis the subarachnoid space is markedly distended by the cerebrospinal fluid, with consequent separation of the enclosed tissues. Furthermore, at the lower level, as a rule, the posterior subarachnoid space is intact, so that the needle first taps the distended sac and there is less danger of perforating the cord.

Posture of the Patient.—The patient should lie well on his side over the edge of the bed. A right-handed operator should have the patient on his left side and vice versa for a left-handed operator. This will allow the right hand to be freely used. The back should be well bowed. The head should be bent as much as possible on the chest. The legs should be flexed on the thighs and the thighs on the abdomen.

Lumbar puncture should never be performed in the erect posture in cases of meningitis. It is extremely dangerous and may be accompanied by collapse and even death.

Selection of Proper Needle.—A large, strong, and pliable needle with large bore should be used. A good steel or, preferably, iridoplatinum needle 4 to 4½ inches in length and 1½ to 2 mm. in diameter will give good results. Most operators prefer a needle with a trochar, as this adds strength to the needle and enables one to clear the lumen of the needle should it be plugged by tissue or fibrin. The edge of the needle should be sharp-cutting, so that it will readily penetrate the tissues, but short-beveled, so that it will have the advantage of a blunt needle in pushing the nerve roots aside as they are met. The short bevel furthermore eliminates the danger of peridural spilling of the cerebrospinal fluid when there is only partial entry of the edge into the spinal theca.

Method and Route of Puncture.—The least complicated and most direct way is the median route. A very satisfactory method is as follows: Select the proper level for the operation, then place the thumb of the left hand firmly in the intervertebral space, pressing it well between the spines and holding it there as a guide for the needle, which is directed at an angle of 45° or less upward and inward between the spines. The needle should be directed rather closer to the upper border of the lower spinal process, in this way avoiding the tubercles which project downward from the lower margin of the lumbar spinal processes. As the membranes are punctured the patient frequently screams and complains of very severe burning, often shooting pains in the back around the abdomen, sometimes in the hip and down the legs. In a moment this pain disappears, but a dull, boring pain at the site of the puncture persists.

The lateral route of puncture has been advocated by some authors, principally on account of the fact that by this route the thick, interspinous ligament can be avoided. A blunt needle can thus be used, and there is less danger of injuring the cord and the spinal nerve roots. This route of puncture, however, requires so much more skill and even in the hands of a practiced operator is apt to be so much more painful that, as a rule, it is far less desirable than the median route.

Accidents During Lumbar Puncture—*Hemorrhage.*—Hemorrhage during lumbar puncture may result either from injury of the epidural veins, which usually occasions the flow of a rather large stream of pure blood through the needle, or from injury of the subdural veins, which, as a rule, simply causes blood tingeing of the cerebrospinal fluid. In the latter condition the cerebrospinal fluid usually clears up after a few moments, but in the former the needle, which has not penetrated the subarachnoid space, should be removed and reinserted, taking care, of course, first to remove the clot from the lumen of the needle. Neither form of hemorrhage, as a rule, is of any consequence.

Accidental Breakage of Needle.—This accident should never happen if a proper needle be selected for the puncture. This needle should be large and powerful. The author has seen a number of instances where the needle snapped off in the middle during an operation after the canal had been reached, caused by a sudden contraction of the muscles of the back. In almost every instance the physician had dissected extensively for the needle, but failed to find it. In none of these cases did the writer attempt to locate the needle. Several patients recovered completely and complained of no symptoms that could be explained by the presence of the needle. The author believes it most advisable in such cases to wait and ascertain how much damage is actually done before instituting radical measures. The dissection of the membrane is an extensive and difficult operation, and should not be attempted unless absolutely indicated.

Specific Treatment of Epidemic Meningitis

The specific treatment of epidemic meningitis varies somewhat in the acute and chronic forms of the disease.

The broad general principle in the serum therapy of acute meningitis is to inject the serum as early as possible after the beginning of the disease, always giving the patient the benefit of the doubt; in treatment always favoring the diagnosis of epidemic meningitis. The serum should be injected at the first puncture. Later the diagnosis may be corroborated by the examination of the cerebrospinal fluid.

Active subdural treatment should be kept up as long as any active signs of the infection are present, either as indicated by clinical signs or by the examination of the cerebrospinal fluid.

The hydrocephalus should be treated at the same time as the specific serum treatment is being administered.

The same attention must be paid to the general measures as in treating any acute infectious disease.

Method and Technic of Administering Antimeningitis Serum.—It has been explained that early diagnosis in treatment is most important. Lumbar puncture should be performed early if only on strong clinical suspicion of meningitis. If the fluid be increased in quantity and slightly opalescent, the serum should be injected. The usual finding in a frank case of meningitis is a large quantity of turbid fluid under considerable pressure. The absolute confirmation of the diagnosis in any case is only made later by bacteriological examination.

After performing lumbar puncture, using the precautions already explained, as much cerebrospinal fluid should be allowed to escape as can be done safely. This is controlled by the condition of the patient, his color, respiration, and pulse, and principally by the coincident observation of the blood-pressure during the operation. As a rule, the cerebrospinal fluid can be allowed to escape slowly until the cerebrospinal fluid pressure comes down to normal, as actually measured by a manometer or roughly gaged by the flow of the fluid, the normal fluid averaging about one drop every three to five seconds. Usually the withdrawal of cerebrospinal fluid is a perfectly safe procedure. The clinical condition, as a rule, is good, and the blood-pressure change is ordinarily insignificant. Most often there is a moderate fall in blood-pressure, varying between 2 and 3 and 10 mm. of mercury. The writer has found by experience that a fall of 10 mm. of mercury in the blood-pressure may be considered a safe guide to discontinue the further withdrawal of fluid. Sometimes the blood-pressure does not change at all during the operation; at other times it may rise.

While the cerebrospinal fluid is being withdrawn the serum should be prepared by warming to body temperature.

The serum is injected through the lumen of the needle under pressure. Two general methods are used: (1) the syringe method; (2) the gravity method.

The syringe method consists simply in the injection of the serum by means of a syringe which is attached to the needle. Most of the lumbar puncture needles manufactured are made to have a standard size handle, so that the tip of the average syringe fits well into the needle.

In the other method serum is injected by gravity. The most simple apparatus used consists of the barrel of a 15 to 25 c.c. syringe used as a funnel attached to a 12 to 14-inch rubber tube about 1/4 inch in diameter, at the end of which is a small metal end piece or adapter which should fit the hilt of the needle. The latter is made by most instrument manufacturers.

The serum is poured into the funnel and made to displace the air in the rubber tube. When the serum appears at the end of the rubber tube it is attached to the needle.

A number of manufacturers have placed on the market a special gravity apparatus, which is fully assembled with the serum in the container and ready for use. The advantage in this is that there is no need of assembling the parts and that there is little exposure of the serum to the air.

It has been explained that the dose of serum is a variable one, and must be carefully controlled in each individual case and at each separate injection. The quantitative method of determining the dose as guided by the quantity of cerebrospinal fluid removed is dangerous, and should not be employed. It has been noted that the blood-pressure falls during the injection of the antimeningitis serum and that the degree of fall may be used as a guide to the quantity of serum that can be safely injected. The writer has been accustomed to have the blood-pressure reported by a special assistant throughout the whole operation, both during removal of fluid and during injection of serum. As a result of observations in many cases, he has found that a total fall of 20 mm. of mercury in a person with an initial blood-pressure of 110 to 120 mm. of mercury indicates that the further injection of serum should be stopped. The same holds true in young people with a high blood-pressure, since the latter in meningitis is most often a direct result of the hydrocephalus, so that patients with an initial blood-pressure of 160 mm. of mercury, or even higher, also cannot usually bear more than a fall of about 20 mm. A slightly greater relative fall in blood-pressure may be allowed in children. The degree of fall in blood-pressure that may be safely allowed during the injection of serum can be fairly well determined by considering a fall of 20 mm. safe for a blood-pressure of 110 mm. of mercury or over for an adult; and for children the same relative fall may be allowed. The utmost caution should be observed especially in the severely toxic, delirious patient.

As a rule, the blood-pressure begins to fall shortly after the injection of the antimeningitis serum has been begun. The amount of fall is dependent upon the quantity of fluid injected and the rate and pressure of the injection. The writer has found clinically, and Dr. Carter has confirmed by experimental observations in dogs, using Ringer's solution for intraspinal injection, that the latter two factors of rapidity and pressure of injection are most important; that a small quantity of fluid injected rapidly under considerable pressure will cause relatively much greater fall in blood-pressure than a large quantity of fluid injected slowly and with little pressure. The great advantage of the gravity method is that the rate and pressure can be much more accurately controlled simply by raising or lowering the funnel holding the serum. The disadvantage of the syringe, furthermore, is that the piston may "stick," and, in exerting force to push it on, a little serum may be suddenly injected under very considerable pressure.

The fall in blood-pressure is usually gradual and progressive up to a certain point, usually to about 20 mm. of mercury in an adult. Beyond this point, if the injection of serum be further continued, the blood-pressure may fall very suddenly and be accompanied by the very severe clinical symptoms of shock, collapse, and even death. Thus 30 c.c. of serum, for example, may be injected into an adult accompanied by a fall of 20 mm. of mercury. If a few more cubic centimeters of serum be injected a very large fall may occur. The author has seen a sudden fall of 100 mm. of mercury in robust subjects when only 4 c.c. of serum were injected after the initial fall of 20 mm. of mercury in blood-pressure.

If the blood-pressure has fallen to a dangerous point before an adequate dose of serum has been injected, one should wait a few minutes. Not infrequently the blood-pressure will rise a bit, and then a little more serum can be injected. If the blood-pressure does not change after the first fall, one may proceed very cautiously. If, on the other hand, the blood-pressure continues to fall, even after the injection of serum has been stopped, under no circumstances should more serum be administered.

Fifteen to twenty minutes may be considered a safe interval of time to allow for the injection of a full dose of serum.

The average dose of serum when controlled by blood-pressure is as follows:

1 to 5 years	3 to 12 c.c. of serum
5 to 10 years	5 to 15 c.c. of serum
10 to 15 years	10 to 20 c.c. of serum
15 to 20 years	15 to 30 c.c. of serum
20 years and over	20 to 40 c.c. of serum (occasionally more)

These doses, though in many instances smaller than formerly used, give very much better results than the larger doses injected without adequate control.

The clinical symptoms accompanying the fall in blood-pressure during the injection of the antimeningitis serum consist principally of deep stupor, severe respiratory embarrassment, and general symptoms of severe shock. The breathing first becomes irregular, slow, stertorous; sometimes very superficial, rapid, and irregular. The color becomes livid; other times, cyanotic. The pupils dilate and there is incontinence of feces and urine.

The pulse quite often remains good at first, but later grows weak, rapid, and irregular; other times, slow and irregular.

With the appearance of symptoms active treatment should at once be instituted. The head of the patient should be raised and as much of the injected fluid removed as necessary. In using the gravity method this can be easily done by simply lowering the container holding the serum. If the blood-pressure rise and the general condition of the patient improve following these measures, a little of the fluid can be reinjected. If the breathing be poor or stertorous, artificial respiration should be actively administered. Atropin in doses of 1/80 to 1/50 gr. and cocain in doses of 1/8 to 1/4 gr. should be injected hypodermatically. Atropin relieves the cardiac inhibition and cocain relieves the respiratory embarrassment. Oxygen, administered under pressure, as used in anesthesia apparatus, is also helpful.

Carter, in his experimental studies on the intraspinal injection of Ringer's solution in dogs, found that the first mechanical effects of the increase in the intraspinal pressure were respiratory embarrassment and marked cardiac inhibition.

Case 1.—Man, aged 22, came under treatment on the second day of his illness. He was severely ill with acute epidemic cerebrospinal meningitis. Blood-pressure was 130; general condition good. Lumbar puncture yielded a very turbid fluid under high pressure. Fifty c.c. of fluid were removed, accompanied by a fall of 5 mm. of mercury in blood-pressure. When the cerebrospinal fluid pressure dropped to normal, further withdrawal of fluid was discontinued. Antimeningitis serum which had been warmed to body temperature was then injected by gravity. The injection of the first 10 c.c. of serum caused no change in blood-pressure. The further injection of serum, however, occasioned a gradual fall in blood-pressure as the larger quantities of serum were injected. When 25 c.c. of serum had been injected, the total fall in blood-pressure had been 18 mm. of mercury. The injection of serum was then stopped and the blood-pressure carefully watched. The fall in blood-pressure, however, continued to a total drop of 22 mm. of mercury. After waiting two minutes and there being no tendency for the blood-pressure to rise, it was decided that a safe dose had been administered and the needle was removed from the spine. The patient's clinical condition was good and he left the table very little the worse for the operation. Eighteen hours later the patient's general condition was very much improved. His blood-pressure at this time was 115. Lumbar puncture yielded a very turbid fluid under very high pressure. The removal of 35 c.c. of fluid caused a drop of 10 mm. The further withdrawal of fluid was therefore stopped and the injection of serum was begun. After 15 c.c. of serum were injected by the gravity method, the total fall in blood-pressure was 20 mm. of mercury. The blood-pressure, too, exhibited a tendency to continue falling in spite of the fact that injection of serum was stopped for the moment. It was decided, therefore, to discontinue the further injection of serum. The patient left the table in good condition.

Steady improvement continued and temperature became normal. Twenty-four hours later another puncture was performed. The blood-pressure at this time was again 135. Lumbar puncture yielded almost a clear fluid under considerable pressure. Fifty c.c. were removed, accompanied by a fall of 5 mm. of mercury. The further withdrawal of fluid was discontinued when the cerebrospinal fluid pressure fell to normal. Serum was injected by the gravity method. Twenty c.c. were injected and blood-pressure fell only 5 mm. It was considered, however, that a dose of 20 c.c. was sufficient in view of the marked clinical improvement and the clearing up of the cerebrospinal fluid. The patient left the table in excellent condition, perfectly conscious and feeling well. From this time on he progressed to an uninterrupted recovery, without further treatment.

Case 2.—Mulatto, aged 25, admitted to the hospital on the sixth day of his illness, violently ill, delirious and severely prostrated. Blood-pressure was 70. Lumbar puncture yielded a thick, purulent fluid. Twenty c.c. were slowly removed without any change in blood-pressure. The injection of serum by the gravity method was almost immediately followed by increasing fall in blood-pressure. The injection of 10 c.c. of serum caused a fall of 15 mm. of mercury in blood-pressure. Thirteen c.c. of serum were followed by a fall of 20 mm. The injection of serum was discontinued. The needle, however, was left in situ for a few minutes while the blood-pressure observations were carefully made. In spite of the discontinuation of serum injection the blood-pressure continued to fall, dropping in all 30 mm. of mercury. At this point the patient's general condition became very bad. His color became pasty; breathing very superficial and irregular. He began to have incontinence of stool. At once the head of the patient was raised and serum was removed from the subarachnoid space. Upon the removal of 8 c.c. of serum the blood-pressure commenced to rise, recovering 10 mm. of mercury; with the rise there was coincident improvement in the general condition of the patient. He was watched for about half an hour, the needle all this time being left in situ. Improvement, however, was steady and he left the table in good condition.

Twelve hours later there was but little improvement in the patient's condition. He was totally unconscious and his general condition was poor. Blood-pressure was 80. Another lumbar puncture was performed. The cerebrospinal fluid was considerably thinner, under very appreciable pressure and still very purulent. Sixty c.c. were removed, accompanied by a rise to 100 mm. of mercury in blood-pressure. Injection of serum was, nevertheless, again immediately accompanied by a rapid fall in blood-pressure. Injection of 20 c.c. of serum occasioned a total fall of

25 mm. of mercury. (This included the gain which occurred during the removal of fluid.) Again the patient's condition became bad. Upon the withdrawal of 5 c.c. of serum there was immediate improvement.

This patient made a recovery after eight injections of serum. At no time was he able to bear more than 20 c.c. of serum without the development of alarming symptoms and very pronounced fall in blood-pressure.

Case 3.—Woman, aged 35, admitted to the hospital after an illness of three days. She was totally unconscious and violently ill. Her blood-pressure was 100 mm. Lumbar puncture yielded a moderately turbid fluid under considerable pressure. Eighty c.c. were removed, accompanied by a fall of 5 mm. of mercury. Serum was then injected by the gravity method. Ten c.c. were injected with no change in blood-pressure. The injection of larger quantities of serum, however, was immediately followed by a steady and progressive fall in blood-pressure; 15 c.c. of serum caused a total fall of 15 mm. of mercury; 18 c.c. of serum a fall of 20 mm. of mercury. In view of the patient's serious condition it was thought desirable to attempt to inject a somewhat larger dose of serum. Twenty-five c.c. of serum were accompanied by a fall of 25 mm. of mercury; 28 c.c. of serum by a fall of 60 mm. of mercury. At this point the patient suddenly stopped breathing. Her head was promptly raised; serum, 12 c.c. in all, was removed rapidly from the subarachnoid space; artificial respiration was instituted; 1/6 gr. of cocain was administered hypodermatically. After a few moments the patient began to breathe; heart action again became good. She left the table in fair condition, though, undoubtedly, the severe shock had left its mark. Fourteen hours later, her condition was worse; blood-pressure was 105 mm. Lumbar puncture yielded a fluid very much the same as the first. Fifty c.c. were removed with a fall of 10 mm. of mercury. The injection of 15 c.c. of serum occasioned a total fall of 20 mm. of mercury. It was decided to discontinue for the moment the further injection of serum, but to leave the needle in situ and to watch the blood-pressure carefully. After waiting five minutes there was no further drop in blood-pressure. Five minutes later the patient recovered 10 mm. of the fall, making the total fall only 10 mm. of mercury. It was decided to continue the injection of serum and 10 c.c. more of serum were administered, again causing a fall of 10 mm. of mercury. After watching the patient for a few minutes to make certain that there would be no subsequent fall in blood-pressure the needle was removed, the patient leaving the table in good condition. This patient died after being treated for three more days.

Observations on Concentrated Antimeningitis Serum.—The principle applied in the refinement and concentration of immune sera consists in the elimination of the albumin and euglobulin from the serum, leaving only the pseudoglobulin, with which protein the immune bodies are closely associated. The method now generally employed is that devised by Gibson in the New York Research Laboratory, subsequently modified and improved by Banzhaf.

While in the Research Laboratory the writer had several liters of antimeningitis serum concentrated, and made some observations on this refined serum in the subdural treatment of epidemic meningitis. Believing that many of the ill effects occurring during the injection could be explained by the quantity of fluid injected, he thought that by reducing the quantity of serum injected, without diminishing the number of immune bodies, he might obtain better results. The serum was concentrated to one-third the original volume. About 12 cases in all were treated at different times with this serum. The dose of serum was one-third to one-half less than the dose of the usual unrefined serum, but the actual number of immune bodies injected was relatively greater.

The results, however, were disappointing; very little, if any, advantage over the unrefined serum was noted, even though full doses were used in a few instances. This may well be explained. The principal virtue of the antimeningitis serum is the production of a local leukocytosis and phagocytosis; this is accomplished most thoroughly when the serum bathes the infected parts freely; a small quantity of serum, though relatively more potent, could not come in as close contact or freely bathe as large a surface and so failed to give as good results as the less potent serum.

Further observations on this subject should be made.

Effect of Preservatives in Serum.—Another feature of the antimeningitis serum might be cited here. All immune sera used therapeutically are rendered sterile and bacteria-free by passage through a Berkefeld filter. Preservatives, such as chloroform and tricresol, are also usually added. In the case of antimeningitis serum, particularly, the use of a preservative is desirable, since an infected serum accidentally injected into the meninges would gravely jeopardize the life of the patient. The Bureau of Hygiene, supervising the Interstate Sale of Biologic Products, has permitted the use of 0.4 per cent tricresol, which has been used in most instances. The writer at different periods has worked with serum without and with tricresol, and, in an attempt to explain some of the severe pain, restlessness, and discomfort which sometimes follow the injection of the antimeningitis serum, made some observations on the effect of serum with different strengths of tricresol when injected into the brain of the rabbit. Serum with 0.4 per cent tricresol made the animal very restless, and sometimes caused convulsive seizures and retraction of the head. Serum with 0.2 per cent or less tricresol did not produce these symptoms.

The writer believes that the large quantities of tricresol permitted as a preservative in the antimeningitis serum are temporarily irritating, though he does not believe, as suggested by some, that this quantity of preservative in antimeningitis serum is very dangerous or has led to death. Sera with 0.4 per cent tricresol injected directly into the ventricles of the brain, in treating posterior basic meningitis, have been as well borne, without ill effects, as when injected by lumbar puncture. A smaller quantity of preservative should, however, be used.

The beneficial effect of the injected serum is indicated very often eight to twenty-four hours after the injection. The temperature may rise for a few hours after the operation, but with favorable response falls later. Quite frequently it becomes normal twenty-four hours after the first dose of serum. The most striking evidence of improvement is in the rapid clearing up of the cerebral symptoms, the disappearance of delirium, and the relapse into a quiet, restful sleep. There is often a prompt improvement in Kernig's sign, the rigidity of the neck, and the other evidences of active meningeal inflammation.

The most important sign of improvement, however, is the clearing up of the cerebrospinal fluid. Before treatment is begun, or if there be no response to serum treatment, the fluid is usually turbid under high pressure, and shows microscopically many pus cells, meningococci, most of the cocci being extracellular and relatively few intracellular. One of the most important functions of the antimeningitis serum is to stimulate phagocytosis. Response to a dose of serum, therefore, is best indicated by the diminution in the total number of meningococci and by the inclusion of the meningococci within the leukocytes; with no improvement there is an increase in the number of meningococci, and most of the organisms are extracellular.

The indications for repeating the doses of serum are the change in the clinical condition of the patient under treatment and the change in the cerebrospinal fluid. Treatment should be actively kept up until either all meningococci have disappeared from the cerebrospinal fluid or until there are only a few meningococci and those all intracellular. Even few extracellular meningococci signify that the dose of serum should be repeated the following day, although the clinical condition of the patient continues good.

If the cerebrospinal fluid shows no meningococci, and the clinical condition of the patient is unsatisfactory, then a dose of serum should likewise be repeated, since it is evident that the infection is still present and that most probably a few extracellular meningococci have been overlooked in the examination.

If the clinical condition of the patient be good, and if the previous fluid had shown few meningococci and those intracellular, then it is perfectly safe to omit the dose of serum that day, repeating it only as is subsequently indicated by the course of the disease.

The average case requires daily injections for three to four days. Severer cases may require a few more doses. After the first three or four doses of serum it is desirable to allow a longer interval between the subsequent doses. Injections on alternate days or even less often, as controlled by the condition of the patient, have the advantage of giving the patient a period of time during which he may not only respond to the previous dose of serum, but also recuperate from the shock of the injection itself. The system, too, is so well saturated with the serum after a few doses that the daily doses are not urgently indicated. Some cases require treatment for a long time—as many as twenty or more doses being necessary.

The intraspinal serum treatment of cases with thick, plastic exudate is difficult and often dangerous. The cerebrospinal fluid is viscid, contains large clumps of fibrin, and is too thick to flow through the lumen of the needle. Injection of the antimeningitis serum under pressure without previously removing the cerebrospinal fluid is very dangerous. One should first attempt to start the flow of the cerebrospinal fluid by gently irrigating with a little sterile salt solution injected through the needle under a little pressure. If this fails two needles may be introduced into the subarachnoid space at different levels so that the solution may be injected at one space and come out at the other. If the latter method proves ineffectual also, one should then administer the serum under pressure, taking great care to inject only a small quantity at one sitting and to note carefully the effect on the blood-pressure during the injection. The treatment may be repeated at more frequent intervals than in the average case. A few doses may be administered at eight-hour intervals. This method of treatment is successful in a fair proportion of cases. After one or two doses of serum the cerebrospinal fluid quite often becomes less viscid and flows well through the lumen of the needle.

Case 4. Thick Plastic Exudate.—Boy, aged 10, admitted to the hospital on the sixth day of his illness. He was violently delirious and had all of the pronounced clinical symptoms of the most virulent form of epidemic meningitis. Blood-pressure, 90. Lumbar puncture yielded a few cubic centimeters of very thick, viscid, creamy cerebrospinal fluid. A few strings of fibrin occluded the lumen of the needle. This was removed with the trochar, but after the escape of a few more drops of fluid the lumen was again clogged. It was then thought advisable to irrigate gently with warm saline solution. Two to three c.c. of saline were injected and allowed to escape promptly. This was attended by but poor results. Serum was then injected under pressure. Six c.c. of serum were immediately followed by a fall of 15 mm. of mercury. The patient became more stuporous, and his breathing became shallow and irregular. Further injection of serum was then discontinued. Eight hours later there was little change in his condition. It was then decided to again puncture. The blood-pressure was now 70. Lumbar puncture again yielded a few cubic centimeters of thick, viscid fluid. Another needle was now introduced into the next lumbar space above. Warm saline was injected in the upper needle and allowed to drain out in the lower. At first, there was no response, but after the introduction of a few cubic centimeters of fluid in this way the flow of cerebrospinal fluid became much freer. In all 15 c.c. of fluid were removed. There was no change in blood-pressure. Serum was then injected. This time a total of 12 c.c. of serum was injected before there was a fall of 15 mm. of mercury with severe symptoms of shock. Injection was then stopped. Twelve hours later the patient's condition had improved considerably. He was more conscious; his general condition was better. Blood-pressure now was 110. Lumbar puncture yielded a very turbid fluid which flowed readily. Forty c.c. were removed, with a fall of 10 mm. of mercury. Twenty-five c.c. of serum were injected before there was a fall of 20 mm. of mercury, when the further injection of serum was discontinued. This patient ultimately recovered.

A similar problem is faced in treating cases with dry canal, giving a so-called dry puncture. Most often the so-called dry puncture really means failure on the part of the operator to enter the subarachnoid space. True dry puncture, however, does occur. It is not infrequently encountered during serum treatment. When accompanied by coincident evidence of clinical improvement the condition may be interpreted favorably and serum treatment omitted at that sitting. Sometimes, however, grave signs of local and general sepsis are seen with true dry puncture. In these cases persistence of the infection, possibly in localized and encapsulated areas throughout the subarachnoid space and within the ventricles, is very probable. Treatment should be continued and serum injected under pressure. Cases like those with thick, plastic exudate often clear up under this mode of serum treatment. The third very important form of dry canal is that present in posterior basic meningitis, in which the subarachnoid space is dry and, through closure of the basal foramina, shut off from its communication with the ventricles of the brain. The latter, in turn, usually contain a large quantity of exudate under considerable pressure. Intraspinal serum treatment of this condition is not only useless, but very dangerous, since the focus of infection, located within the ventricles of the brain, is not reached by the injection into the subarachnoid space; the fluid so administered under pressure would cause grave pressure symptoms. The special treatment for this condition will be described later.

Serum Treatment of General Bacteriemia Immediately Preceding and During the Course of Meningitis

It will be explained further on that meningitis begins as a local nasopharyngitis, which in a certain percentage of cases is followed by general bacteriemia. The latter lasts on the average of between eight and thirty-six hours, and may terminate in one of several ways. It may terminate in recovery, as seen in the so-called aborted cases during an epidemic of meningitis. It may result in death, as in the cases of terrific general sepsis, often accompanied by very profuse petechial and purpuric eruptions, which show slight or no signs of meningitis, but which terminate in death very shortly after the onset of the disease. These are the true fulminating cases. Most often, however, the general bacteriemia after a certain number of hours is succeeded by localization of the infection in the meninges, followed by the classical infection of epidemic meningitis. The general bacteriemia in these cases dies out to a very great extent a short time after the onset of the meningitis proper. A moderate bacteriemia persists, however, in a fair proportion of cases.

The first condition to be met, therefore, is the premeningitic stage. The rapid fatal outcome of the fulminating cases may be prevented in some instances, and the average cases which run the usual course of meningitis may be considerably improved, so that when meningitis proper sets in the infection will be much milder and to a degree under control.

Correct, accurate diagnosis during this important period of premeningitis is so very difficult that, unfortunately, this stage is often overlooked. During epidemics of meningitis, however, physicians should be on the lookout for the disease. Careful weighing of symptoms during an epidemic will, in some cases, permit a tentative diagnosis.

The principal symptoms of this stage may be grouped under two headings: (1) general sepsis, with history of exposure; (2) hydrocephalus. The symptoms of general sepsis, evidenced by the chill, fever, and prostration, are very much the same here as in other forms of general sepsis. Most significant manifestations, however, are severe general petechial eruptions or purpura, crops of herpes on the face, conjunctivitis, together with the laboratory findings. Blood examination demonstrates a moderate leukocytosis with high relative polynucleosis. Examination of the secretion of the herpes quite often exhibits a few meningococci (Gram-negative diplococci), and examination of the urine will in a small percentage of cases demonstrate large numbers of Gram-negative diplococci. Blood culture, while very often positive during this stage, is, of course, of no value for rapid early diagnosis.

The early presence of hydrocephalic symptoms can be explained by the special affinity of the meningococcus for the meninges. This affinity of the toxic products during the stage of general bacteriemia probably accounts for the early irritation and collection of clear fluid within the ventricles and subarachnoid space and the subsequent localization of the meningococcus in the meninges with the onset of the true meningitis. The significant clinical symptoms due to this condition are the violent, persistent headache, which cannot be explained by the usual causes; the early, repeated, explosive vomiting, which is not accompanied by evidence of any gastro-intestinal disorder and cannot be controlled by local treatment; the early hyperesthesia, irritability, and photophobia; the dilated, sluggishly responding pupils, the tenderness at the angles of the jaws and the presence of the bulging fontanel in young children or the Macewen sign in the older, and, most important, the irregular pulse and respiration. Treatment of this condition, even on suspicion, should consist of lumbar puncture with removal of a large quantity of exudate followed by the injection of a small dose of serum into the subarachnoid space. A larger dose of serum up to 100 c.c. should at the same time be injected subcutaneously or intravenously. The general bacteriemia will, in a measure, be controlled by the injection of the serum into the general circulation, and the hydrocephalus will be relieved by the removal of fluid. The injection of a small dose of serum into the subarachnoid space also helps to take care of any infection which may already be localized in the meninges.

Case 5.—Girl, aged 19, was seen by the writer 18 hours after the beginning of symptoms. She did not appear very ill and had only slight fever. She complained of persistent headache, had occasional attacks of projectile vomiting, felt dizzy, was irritable and restless, and complained of pain at the nape of the neck. The pupils were widely dilated and responded very sluggishly to light. She had a crop of herpes on the upper lip and had a few petechial spots over the extremities. These symptoms of moderate hydrocephalus and mild sepsis, occurring during an epidemic of meningitis, warranted a tentative diagnosis of the first or premeningitic stage of meningitis. Many of the active signs of meningitis were missing. Neck rigidity was absent, as was also the Kernig sign and many of the other classical signs of epidemic meningitis. Lumbar puncture yielded a clear fluid under very high pressure, 45 c.c. of fluid being removed. Fifteen c.c. of serum were injected intraspinally. At the same time 30 c.c. of serum were injected underneath the skin. An examination of the cerebrospinal fluid showed a slight increase in protein content, 50 cells per c.mm., most of the cells being lymphocytes, and the examination of the smear showed a few Gram-negative extracellular diplococci, which, however, failed to grow in culture. The diagnosis was apparent. The disease was either in the premeningitic stage (stage of general bacteriemia) or just at the very beginning of the meningitic stage. The presence of a few extracellular organisms in the cerebrospinal fluid, however, did not necessarily mean that the bacteria had already localized in the meninges, since these bacteria could be explained by the coincident general bacteriemia.

This patient made a prompt, uninterrupted recovery and was discharged as well four days later without any further treatment. The prompt recovery here could be explained by the treatment of the general bacteriemia through the subcutaneous injection of serum, the treatment of the possible beginning of the local infection in the meninges by the serum injected into the subarachnoid space and the relief of hydrocephalus with the removal of cerebrospinal fluid.

Case 6.—Woman, aged 45, admitted to the hospital in a state of complete collapse after an illness of 8 hours. She was cyanotic and almost pulseless. She was perfectly conscious, however, and complained only of a severe headache, vertigo and vomiting. Her neck was limber and Kernig's sign was absent, but the pupils were widely dilated and Macewen's sign was present. She was also exquisitely tender upon pressure at the angles of the jaws. Her body was covered with a very profuse petechial eruption. Temperature was subnormal. An examination of the urine showed many pus cells and many extracellular and intracellular Gram-negative diplococci. (A history of gonorrhea could be absolutely excluded.) Blood examination showed white blood-corpuscles, 12,000; polymorphonuclears, 80 per cent.

This case was evidently a severe, fulminating type of epidemic meningitis. The terrific onset, prostration, with the profuse petechial eruption, accompanied by the presence of Gram-negative diplococci in the urine, indicated a severe general bacteriemia. The symptoms of headache, vomiting, dilated pupils, and the Macewen sign indicated moderate hydrocephalus. Lumbar puncture was performed, and 20 c.c. of absolutely clear fluid under moderate pressure was removed. In view of the severe prostration, it was thought inadvisable to inject serum. Sixty c.c. of serum was injected subcutaneously; active stimulation for shock was also promptly applied. For a period of 18 hours the patient needed constant attention; two intravenous infusions of saline solutions were necessary, with other very active stimulation. Her general condition then suddenly improved; color became better, heart action much stronger. Temperature, however, now rose to 103°, and more active signs of meningitis appeared. The neck became very rigid, Kernig's sign marked, and Macewen's sign more pronounced. Lumbar puncture yielded a very turbid fluid under high pressure, 60 c.c. being removed. Thirty c.c. of serum were injected. The examination of the cerebrospinal fluid showed many diplococci, mostly intracellular. The urine, however, now failed to show any organisms whatsoever. This patient recovered after three more doses of serum, though joint involvement, which occurred on the third day of the illness, persisted for a few weeks.

Had serum been injected intraspinally at the first lumbar puncture it is possible that the severe subsequent meningitis might, in a measure, have been prevented. The patient's general condition, however, absolutely prohibited the intraspinal injection of serum at that time. The writer is inclined to believe, furthermore, that little if any good would have resulted, since it was fairly evident that at the time, at least, the patient was suffering not from meningitis, but from a severe, overwhelming, general bacteriemia. This was treated and partly controlled by the subcutaneous injection of the serum. It would have been more desirable to inject the serum intravenously, but this was not done on account of the patient's precarious condition.

The treatment of general bacteriemia during the course of meningitis is, in a measure, controlled by the serum, which is injected subdurally, since it has been explained that sera injected into the subarachnoid space are excreted into the general circulation very quickly.

If one be unable, however, to inject suitable doses of serum into the subarachnoid space, the general bacteriemia may be coincidentally treated by injection of the serum subcutaneously and intravenously.

Treatment of Hydrocephalus during Acute Stage of Meningitis

While the condition of hydrocephalus is very important, it does not, as a rule, require any special treatment during the acute stage of meningitis, since during the usual course of serum treatment hydrocephalus is relieved at the time of each serum administration. The cerebrospinal fluid is first withdrawn before serum is injected. The severity of the hydrocephalus, too, is in proportion to the degree of the local sepsis. Thus, when a dose of serum is necessary for the local infection, coincident treatment for hydrocephalus is also indicated. Occasionally, however, very severe pressure phenomena may set in a few hours after an injection of serum. The patient may become very stuporous or totally unconscious, the breathing growing very stertorous and irregular, the heart action bad. Lumbar puncture for relief of hydrocephalus without serum injection is then indicated. Prompt relief usually follows.

Case 7.—Boy, aged 19, ill 3 days with epidemic meningitis. There was fair response under serum treatment, but 8 hours after the second dose of serum the patient suddenly developed an alarming group of symptoms. He became wildly delirious and unmanageable; his heart action became rapid and irregular; breathing became very rapid and superficial, at times slowing down with long periods of apnea. The pupils were widely dilated and slight internal strabismus developed. Macewen's sign was very pronounced. It was evident that the patient was suffering from a sudden exacerbation of severe hydrocephalus. The temperature was lower and the previous improvement of septic symptoms pointed against sepsis as being the possible cause of these symptoms, although, of course, an aggravation of the local cerebrospinal infection would probably also be accompanied by an increase of the hydrocephalus. The occurrence of the symptoms, however, a few hours after the injection of the serum seems to indicate that the hydrocephalus might be traced to the injection of the serum proper—a condition which is occasionally seen a few hours after the injection of the antimeningitis serum. Lumbar puncture was performed and 85 c.c. of cerebrospinal fluid, moderately turbid, under very high pressure was removed. No serum was injected. The patient promptly became quiet, the delirium subsided and he fell into a quiet, deep sleep. Breathing became regular, heart action good, color excellent. He woke 8 hours later, perfectly conscious, with a normal temperature, well on the road to recovery. He required one more dose of serum 48 hours later, but after that made an uninterrupted recovery without further treatment.

A varying degree of hydrocephalus, due to the collection of a bacteria-free exudate, usually persists for a few days or longer after the infection proper has cleared up under serum treatment. Sometimes the hydrocephalus is severe and pressure symptoms distressing. Here again lumbar puncture with removal of cerebrospinal fluid gives prompt relief.

A tardy convalescence will often immediately improve after this simple measure. During the course of serum treatment, if only a few bacteria be present, but relatively large quantities of fluid, it may be well to tap one day and, if necessary, inject serum the next day. Relief of the local pressure with improvement of the local circulation will often enable the meninges to take care of the remaining bacteria without necessitating the special injection of serum.

The average case of meningitis requires daily administration of serum for three or four days. If improvement be steady, at the end of this time the cerebrospinal fluid will often be clear but considerable in quantity. It may be sterile or have only a few bacteria. In either instance it is often preferable simply to tap the fifth day if pressure symptoms so indicate, and not inject serum. If any septic phenomena be still present a day later a dose of serum may then be injected.

TREATMENT OF SUBACUTE AND CHRONIC MENINGITIS

For purposes of study chronic meningitis may be divided into the severe form, the mild form, and posterior basic meningitis.

The severe form of chronic meningitis is a continuation of a severe acute meningitis in a chronic state. Infection is persistent and hydrocephalus severe. Treatment should be along the lines set forth for the acute stage. It may be well to allow longer intervals between the doses of serum and in the period between the doses to tap and relieve pressure.

The meningococcus vaccine, preferably autogenous, may be used. A small dose of 50,000,000 to 100,000,000 killed meningococci should be injected at first and gradually increased to the larger doses until response is observed. Intervals between the doses of vaccine depend upon the reaction and the response. As a rule, three-day intervals are satisfactory.

Case 8.—Girl, aged 14, was seen by the writer 2½ weeks after the beginning of her illness. During this period she had had 2 doses of serum, but active intraspinal treatment had not been administered. She presented all of the usual signs of meningitis with pronounced hydrocephalus. In addition she was markedly emaciated, very stuporous and appeared to be blind. Daily lumbar puncture with removal of cerebrospinal fluid, followed by the injection of serum, was performed for the next 7 days. There was temporary improvement after the first few treatments; the patient became more conscious, and appeared to see. After a week, however, she lapsed into her former state. Treatment was now administered every other day, then every third day. Hydrocephalus was pronounced and the fluid remained persistently turbid with extracellular and intracellular meningococci in great numbers. She was evidently suffering from the severe form of chronic epidemic meningitis. After 10 days of this treatment meningococcus autogenous vaccine was made and treatment begun, at first with 50,000,000 killed organisms, later with larger doses until 1,500,000,000 killed meningococci were injected every 5 days. The patient lingered for 1 month and finally died.

Case 9.—Man, aged 35, admitted to the hospital 1 week after his illness. He had had 1 dose of serum injected intraspinally on the fourth day of his illness with no subsequent treatment. The diagnosis was evidently that of a moderately severe case of epidemic meningitis. He was actively treated, being injected daily for 4 consecutive days with a suitable dose of antimeningitis serum. The cerebrospinal fluid cleared up markedly, though a few extracellular meningococci persisted and a moderately severe hydrocephalus continued. He was given 2 more doses of serum at 48-hour intervals and then apparently seemed to be well on the road to recovery. All bacteria had evidently disappeared, though a moderate hydrocephalus persisted. He continued well for 4 days, no treatment being given during this period. He then suddenly began to complain of severe headache; he vomited and his temperature shot up to 102° F. His general condition, however, was good, the neck only slightly rigid, the Kernig slight. Macewen, however, was marked. Lumbar puncture yielded an almost clear fluid under very high pressure. Sixty c.c. were removed. Twenty c.c. of serum were injected. An examination of the cerebrospinal fluid showed a few extracellular meningococci in smear but no growth in culture. After this treatment there was a prompt response and the patient continued well for a week, when once more a similar group of symptoms appeared. Again lumbar puncture was performed. This time 100 c.c. of clear cerebrospinal fluid was removed and 15 c.c. of serum later injected. The examination of the sediment demonstrated a few clumped bodies which looked very much like clumped meningococci. Culture was sterile.

We were evidently dealing, therefore, with a mild case of chronic meningitis of which the chronic hydrocephalic symptoms predominated and with it a mild, persistent infection continued. Vaccine treatment was then instituted, using an autogenous vaccine. He was injected at 3-day intervals with 100,000,000 killed meningococci. No further symptoms developed and after one month the patient was permitted to go home.

Milder Form of Hydrocephalus.—This form consists principally of a moderate hydrocephalus with a mild persistent infection. The hydrocephalus should be treated by repeated regular tap with simple removal of fluid daily or every other day or less often, depending upon the pressure symptoms. Occasionally tap with removal of fluid will give comfort and relief of all symptoms for a period of a week or longer; a puncture at that time will again yield similar results. It is dangerous, however, to allow the long intervals of a week between the punctures, since these cases are apt to lapse gradually into severe emaciation, increasing stupor, palsies, and finally death. Treatment should be more active and simple drainage or injections made at shorter intervals.

Sepsis should be treated by occasional injection of serum. The guides for repeating the dose are found chiefly in the change of the cerebrospinal fluid. With improvement there is a reduction in the number of meningococci, their inclusion within the cells, and finally their total disappearance. Frequent injections of serum are not as well borne in this, the chronic form of meningitis, and longer intervals of a few days must be allowed between the different doses.

Vaccine in this condition is very helpful, and will often easily take care of the slight, persistent infection. The general rules for administering the vaccine are the same as explained for the severe form of chronic meningitis.

Posterior Basic Meningitis.—This condition consists of the shutting off of the basal foramina, through which the fluid in the subarachnoid space communicates with that in the ventricles. The infection in the ventricles becomes localized and hydrocephalus becomes extreme. The inflammation in the subarachnoid space becomes negligible so that, while at first a few cubic centimeters of infected fluid may be obtained by lumbar puncture, after a few days lumbar puncture either results in a dry tap or yields only a few drops of sterile fluid. Occasionally the condition occurs during the acute stage of meningitis; most often, however, it occurs late in the disease either during the chronic stage or during the apparent convalescence from the acute stage of meningitis. Pressure symptoms are most severe and form the striking feature of the clinical picture; septic symptoms are relatively insignificant. At first the fluid encapsulated within the ventricles is infected and contains many meningococci. This condition may persist to the very end. Most often, however, after a few days, the fluid within the ventricles becomes spontaneously sterile, though the quantity of fluid does not diminish. The rapid reaccumulation of fluid has partly been explained by the occasional thrombosis of the veins of Galen with the resulting hyperemia.

The first consideration in treatment is to recognize the futility and danger of intraspinal injection of serum. The only possible hope, slim though it may be, is by direct tapping of the ventricles. The object of treatment and the indications are the same as in the intraspinal treatment of the average case of meningitis. In the latter puncture removes cerebrospinal fluid from the subarachnoid space, and from the ventricles of the brain; the serum injected bathes the infected meninges and ventricles. In posterior basic meningitis the infection is localized in the ventricles and can only be reached by direct ventricular puncture. After ventricular puncture the indications for simple removal of cerebrospinal fluid or injection of antimeningitic serum are the same as in the intraspinal treatment of the usual acute case of meningitis.

The instruments for the operation of intraventricular puncture are the same as for lumbar puncture. One must be especially careful to keep the trocar of the needle in situ while inserting the needle through the brain tissue, since otherwise the lumen of the needle will become clogged with brain tissue.

In children with open fontanel the operation is relatively simple. The ventricles are very much dilated and the cortex thin, so that a needle introduced in almost any direction will easily enter the cavity of the ventricles. The extreme lateral border of the anterior fontanel should be selected. The needle should be directed downward, slightly backward and inward to a depth of 2 to 4 cm. or more. When the needle enters the cavity it usually "gives." The head should be turned to the side operated. Gentle elevation of the trunk allows more complete drainage. The skull must be trephined in older individuals with closed fontanel. Either Kocher's or Keene's point for trephining may be selected. Kocher's operation is more simple and direct. Like the puncture through the open anterior fontanel, the needle traverses the frontal lobe. The point of selection for trephining is situated 2½ cm. anterior to the central fissure—a point lying somewhat in front of the bregma. The needle should be introduced in a direction slightly downward, backward, and inward to a depth of at least 4 or 5 cm. before the ventricles are reached. At this point the ventricle is broad, extending fully 2 cm. from the middle line; there is practically no risk of hemorrhage during the passage of the needle. After the operation the skin flap is closed over and subsequent punctures are made through the scalp.

Keene's point is preferred by some on account of the better drainage. The site of election is at a point corresponding with the posterior end of the temporal line about 3 cm. behind and an equal distance above the external auditory meatus. At this point the needle enters the posterior part of the first temporal convolution, and should be directed toward the summit of the opposite pinna. At a depth of about 5 cm. the ventricle will be entered at its widest part, that is, where the lateral and posterior cornua are given off from the body of the ventricle at the posterior end of the thalamus. This procedure, like the simple puncture in babies, is well borne.

As a rule, the communication between the two ventricles remains patent, so that tapping one ventricle drains the other also. Drainage, however, of the opposite ventricle is incomplete, so that better results have been obtained by puncture of both ventricles—one at a sitting.

The condition of hydrocephalus is relieved by the simple removal of fluid. If the fluid is clear and sterile no further treatment is necessary. Puncture of either ventricle should be made daily, every other day, or less often as indicated by pressure symptom. A fine catheter or catgut may be left in the ventricle for drainage. If the fluid be infected and contain meningococci, serum treatment should be administered the same as during the lumbar intraspinal operation. The same technic and precautions must be observed during this operation as during the intraspinal operation. The injection of moderate doses of serum is very well borne.

The condition of posterior basic meningitis is usually a chronic one, and lasts very often a few weeks, so that as many as twenty treatments may have to be administered. The condition is almost hopeless, even with treatment. Treatment, however, must not be deferred on that account. Even ½ per cent of recoveries warrants these therapeutic measures. A few cases of recovery following this method of treatment have occurred. Fisher reported one case in 1910. In 1912 two cases recovered, one in Forth Worth and the other in Kansas City.

Some have advised gentle irrigation of the ventricles with saline solution before injecting the antimeningitis serum. The writer has employed this in some cases, and sees in it little or no advantage. In most instances the fluid is clear and sterile, and in others it is only slightly purulent and flows freely through the needle. Complete drainage, therefore, is easily attained by puncture and little gained by irrigation.

Haynes has conceived the idea of treating certain hydrocephalic conditions by draining the fluid from the hydrocephalic cavity into one of the easily accessible sinuses, attempting to reproduce the course of the fluid into the blood-stream. The operation termed by him cisterna sinus drainage, seems to be based on careful experimental and clinical observation and is worth trying in cases of posterior basic meningitis, where the more simple methods do not give immediate encouragement.

Dangers of the Intraventricular Puncture.—Two dangers must be considered: injury to the vital centers and hemorrhage. As a rule, neither danger need be feared if care be employed to follow the technic described. Danger of hemorrhage lies principally in injury of the pial vessels or the choroid plexus. Puncture at either Kocher's point, Keene's point, or through the lateral border of the open anterior fontanel may cause hemorrhage, rarely severe bleeding. Hemorrhage with subsequent localized palsies, however, sometimes occurs in spite of all precautions.

Neither this danger nor injury to vital centers is sufficiently imminent to contra-indicate the operation. Direct ventricular puncture is the only hope for these unfortunates, and it should always be done. The cited cases of recovery establish the correctness of this procedure.

Case 10.—A negro child, aged 12 months, was admitted to the hospital a week after the onset of its illness. The child was unconscious, but her eyes were wide open and staring. Opisthotonos was extreme, the head touching the buttock. The sutures were wide open and the anterior fontanel markedly bulging. There were tonic spasms and contractures of the extremities with occasional severe general convulsions. Lumbar puncture yielded dry tap at three different levels. Diagnosis of posterior basic meningitis was made.

The ventricle was then tapped through the right lateral border of the anterior fontanel. About 30 c.c. of purulent fluid which subsequently demonstrated many extracellular and intracellular meningococci were removed. Twenty c.c. of serum was injected into the ventricles with little change in blood-pressure or the patient's general condition. On the following day the other ventricle was tapped and 25 c.c. of purulent fluid, in which many meningococci could still be demonstrated, were obtained. Serum here also was injected directly into the ventricles, 20 c.c. being well borne. On the third day the right ventricle was again tapped and 20 c.c. of a less turbid fluid removed. It was thought that possibly the left ventricle was not sufficiently well drained through the right ventricular puncture. Leaving the needle in situ in the right ventricle another needle was introduced through the left lateral border of the anterior fontanel into the left ventricle. About 10 c.c. of fluid were removed. This demonstrated that drainage was incomplete. Serum was then injected into the right ventricle, the needle being left in situ in the left ventricle, it being thought for the moment that possibly the communication between the ventricles was shut off and that it might be desirable to inject serum into the left ventricle also. Twenty c.c. of serum was injected into the right ventricle. After 10 c.c. was injected, fluid began to appear through the other needle and as the larger quantities of serum were injected into the right ventricle the fluid began to flow freely from the left needle. This proved that there was free commmunication between the two ventricles. This patient had in all 16 treatments. After the sixth treatment the fluid had entirely cleared. No bacteria could be demonstrated in the ventricular cerebrospinal fluid. Severe sterile hydrocephalus, however, continued and pressure signs were pronounced. In subsequent ventricular punctures the cerebrospinal fluid was removed, but no serum injected. After the removal of the fluid there was improvement in the patient's condition for a period varying between 24 and 72 hours, but after that relapse again occurred. For a period of a few days a drain was left in both ventricles. This, however, did not do any good. One month after admission to the hospital the patient died in a severe general clonic and tonic convulsion.

This case illustrates posterior basic meningitis as an early complication of acute meningitis. The cerebrospinal fluid in the ventricles was badly infected. The latter promptly improved under serum treatment, but hydrocephalus was unaffected, ultimately causing death.

Case 11.—Child, aged 10 months, was stricken with an attack of acute epidemic cerebrospinal meningitis. Treatment was instituted on the second day of the illness and actively continued. After 4 doses of serum the child was apparently improving and well on the road to convalescence. Instead of rapidly convalescing, as is usual, the child appeared listless, stuporous, and continued to waste away rapidly. The cerebrospinal fluid was clear and failed to show any bacteria. All active signs of meningitis had also disappeared.

Two weeks after the onset of the disease the child lay in a semi-stuporous state, her eyes wide open and staring. Her head began to be drawn back and after a few days she developed severe opisthotonos, the head almost touching the buttocks. Clonic and tonic convulsions appeared and there were persistent tonic spasms of the hands. The fontanel began to bulge again.

Posterior basic meningitis of the sterile type was diagnosed. Lumbar puncture at three different levels yielded a dry tap. A needle was introduced through the right lateral border of the anterior fontanel into the right ventricle; about 45 c.c. of clear, limpid fluid was removed. Examination failed to show any meningococci either in smear or in culture. The right and left lateral ventricles were alternately regularly tapped at 24, 48 or 72-hour intervals as necessary for a period of 2 weeks. Each tap was followed by a prompt improvement of many of the symptoms. Opisthotonos became less marked and the child appeared to be able to see again. Convulsions ceased and tonic spasms relaxed. Progressive, rapid emaciation, however, continued, and after 3 weeks the child expired.

This case well illustrates the usual form of posterior basic meningitis —the type where the infection has been totally destroyed both in the ventricles and subarachnoid space. Hydrocephalus is extreme and persistent, and in most instances resists all treatment.

Author's Case of Recovery (Case 12).—Child 11 months old was seen by the writer in consultation with Dr. Saulsberry. There was a history of 3 weeks' illness conforming in every respect to epidemic meningitis. First lumbar puncture yielded a very large quantity of turbid fluid showing a few meningococci. The usual serum treatment was immediately instituted. Puncture and serum injection were repeated twice. There was very marked clinical improvement, but still evidence of a pronounced hydrocephalus and a few meningococci could still be found when the parents decided that the child was very much better and opposed further treatment. The writer did not see the child again until 2 weeks later, when Dr. Saulsberry reported that the child was having severe convulsions and he thought was about to die. The child at this time presented a typical picture: a peculiar facies, the eyes open, staring with lids retracted; the face blank and expressionless, disturbed at times by a grimace accompanied by a shrill hydrocephalic cry. The head was markedly extended and the body showed extreme form of opisthotonos, the head almost touching the buttock. The child did not seem to see and could not swallow. The head was markedly enlarged, the sutures widely separated, anterior fontanel markedly bulging; the head felt like a bag full of water. There was marked rigidity of the whole body and persistent convulsive spasm of the upper extremities, which were extended with hands clenched and lower extremities with the feet extended and toes flexed. There was a marked tâche cérébrale. Heart action was rapid and intermittent, but at times during the day it was slow and intermittent. Respirations were slow, irregular, with long periods of apnea, breathing corresponding best to the Biot type. Reflexes were markedly exaggerated. The child had been lying in this "hypnotic state" for several days. Occasionally there was explosive projectile vomiting without exciting cause.

The child presented evidence of terrific hydrocephalus; the peculiar facies, the staring eyes, the retracted lids, the extreme opisthotonos suggested that we were dealing with posterior basic meningitis.

Lumbar puncture made at two levels yielded a few drops of cerebrospinal fluid. A ventricular puncture was then done.

The right ventricle was first tapped, 50 c.c. of slightly turbid cerebrospinal fluid was removed under very high pressure and 20 c.c. of serum containing 0.2 per cent of tricresol preservative was injected. There was a fall of 10 mm. of mercury in blood-pressure on the removal of the fluid, but no change on injecting the serum. The next day the condition was somewhat improved, convulsions were controlled, but other pressure signs were again present. The left ventricle was tapped and 80 c.c. of slightly turbid cerebrospinal fluid was again removed and 20 c.c. of serum injected with blood-pressure change as on the previous day. The cerebrospinal fluid obtained the first day showed a moderate number of pus cells and a few meningococci, extracellular and intracellular. The second fluid showed only intracellular meningococci.

Two days later the right ventricle was again tapped; 60 c.c. of clear fluid was removed. No meningococci were found. The child showed considerable improvement though he still did not seem to see, opisthotonos less marked, pulse and respiration less irregular. The child nursed, had no temperature, cried more normally and in general was much improved.

The parents again decided against further treatment. The child continued to improve, and 2 weeks after the last puncture all the pressure signs and opisthotonos had disappeared, the child could see, and nutrition improved.

I did not see the child until 2 months later when Dr. Saulsberry called me on account of attacks of dyspnea and cyanosis with loss of consciousness, which first appeared a month previously, coming on at intervals of a few days but in the previous week several times daily.

The child presented a most astonishing picture. He was bright, stout, and had grown tremendously. In 2 months he had put on the growth that usually requires a year and a half. He was active, playful, could see well, and had developed mentally almost in proportion to his skeletal growth. The head was large and showed signs of hydrocephalus. There was also evidence of a large thymus. I interpreted the condition as due to a persistent hydrocephalus and attributed the excessive skeletal development to a possible pituitary involvement. Lumbar puncture was performed and 60 c.c. of clear fluid was removed. *The puncture proved that the communication between the ventricles and subarachnoid space had been reëstablished.* The child did not have convulsions until 3 days later. For the next 2 weeks convulsions occurred once every few days and seemed to be generally improved after the puncture.

The last the writer heard of the child, 6 weeks later, the convulsions were less frequent and there was continued good development.

This case is of importance as demonstrating the value of therapy. The recovery was complete with the exception of subsequent convulsive seizures. The complicating hyperpituitarism and thymic growth were of unusual interest. It also shows that communication between ventricles and subarachnoid space can be reëstablished. This may be explained when the closure is due to an inflammatory exudate.

GENERAL TREATMENT OF MENINGITIS

The fact that one is dealing with delirious and unconscious patients renders the general treatment important.

The general nutrition should have careful attention. Fluids and nourishment should be given abundantly. A liberal soft diet is well borne.

The bowels, which tend to be constipated, should have careful attention. Laxatives and enemas should be used as necessary.

The bladder needs special attention. Paresis, with loss of control of the vesical sphincter, is common. In most instances the apparent incontinence which is recorded is really an overflow of a little urine from an overdistended bladder. Restless and delirious patients will often become quiet and sleep after catheterism. It is a safe rule during the period that the patient is irresponsible to order regular catheterism of the bladder.

Restlessness and delirium are very much benefited by the ice helmet and warm sponging. It is questionable whether or not the ice helmet has any virtues other than its sedative action.

The usual sedatives of bromid, chloral, combinations of phenacetin, aspirin and codein, and codein and veronal are usually necessary during the acute period of the disease. Morphin is often imperative. Sometimes hyoscin must be used.

The pain and general restless symptoms after puncture with injection of serum are benefited by the local application of ice-bags or hot-water bags at the site of the puncture. Raising the head of the patient will often relieve the headache and vertigo which quite often follow. Morphin is often necessary during or immediately after the operation.

Some workers have recommended that the foot of the bed be raised about twelve inches, the purpose being to aid the better circulation of the injected serum. This procedure is often followed by complaint of headache and vertigo. Furthermore, the writer has found nothing gained by this expedient, judging by the comparative studies of cases in which it has been employed as against those in which the patient has been kept level.

Internal Medication.—Some observers have demonstrated that urotropin, taken by mouth, is secreted into the cerebrospinal fluid, where it has some disinfecting properties. Urotropin alone, without other treatment in epidemic meningitis, is not curative, but as an aid has some value. Large doses should be prescribed; not less than 40 to 60 gr. daily administered in large quantities of water are advised.[1]

General Treatment of Convalescents.—Patients must not be allowed out of bed too soon on account of the persistent hydrocephalus. Iodid internally, iron and other tonics, together with liberal diet, help.

TREATMENT OF COMPLICATIONS

The complications of meningitis are many and dangerous. They may be grouped into two large divisions. In the one are included all those complications resulting directly from the local cerebrospinal inflammation with destruction of tissue, including changes in mentality, various paralyses, eye complications, and deafness. The second division consists of those complications due to the complicating general meningococcus sepsis present before and during the course of meningitis. This includes the common joint complications, septic pneumonia, pyelitis, general meningococcus sepsis, meningococcus endocarditis, middle-ear infection, some of the eye infections, phlebitis, and neuritis.

Treatment of Changes in Mentality.—The commonest change in mentality following meningitis consists in a change from an amiable, pleasant personality to one that is irritable, vicious, and unreliable. These changes most often clear up spontaneously without special treatment. Sometimes mild, persistent, simple hydrocephalus is the cause. In these cases puncture with relief of pressure helps considerably.

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[1] The irritant action of urotropin on the kidneys should be borne in mind. If hematuria develops the drug may be temporarily withdrawn.—Editors.

Temporary or persistent imbecility is fortunately a less common complication. These cases offer much less hope of improvement. Persistent hydrocephalus, however, in these cases, as in the former, is very often an important influence. Careful examination, therefore, should always be made for evidence of hydrocephalus and, if present, simple lumbar puncture should be done and fluid removed.

The most severe and dreaded complications under this heading are the cases of severe meningomyelo-encephalitis. The clinical picture is one of lingering, absolute imbecility, with stupor, paralyses, occasional convulsions, incontinence, gradual wasting, with ultimate dreadful emaciation, bed sores, and finally death after a period of weeks, months, even a year. The pathological condition is one usually of meningomyelo-encephalitis, with moderate hydrocephalus. Treatment should be along the following lines: (1) occasional tap, with relief of hydrocephalus; (2) occasional injection of serum if a mild, persistent infection be present; (3) the use of meningococcic vaccine. These cases, however, offer but little hope; almost all die.

Paralyses Complicating Meningitis.—This is one of the more frequent complications. Most often the palsies are cerebral in origin, and consist of monoplegia or hemiplegia. Less often palsies are peripheral in origin. The latter sometimes are the direct result of lumbar puncture —high lumbar puncture with injury of some of the centers of the cord. In either instance the prognosis is fair, especially in young individuals. There is no specific treatment. The same general measures should be employed as in paralysis from other causes.

Eye Complications.—The great frequency of eye complications in meningitis may possibly, to a very great extent, be explained by the structure of the optic nerve and its intimate association with the brain. It is frequently described by anatomists as a prolongation of the brain substance rather than as an ordinary cerebrospinal nerve. As it passes from the brain it receives sheaths from the cerebral membrane, a perineural sheath from the pia mater, an intermediate sheath from the arachnoid, and an outer sheath from the dura mater, which is also connected with the periosteum as it passes through the optic foramen. These sheaths are separated from each other by spaces that communicate with the subdural and subarachnoid spaces respectively. The innermost or perineural sheath sends a process around the arteria centralis retinæ into the interior of the nerve, and enters immediately into its structure. Thus inflammatory affections of the meninges or of the brain may readily extend along these spaces or along the interstitial connective tissue in the nerve.

The intimate association between the infected meninges and the ocular nerve may thus readily explain the frequent eye suppurations in epidemic meningitis.

Another possible mode of infection in meningitis may be the severe general bacteriemia (sepsis) which is frequently present in the acute stages of the disease.

The most common eye complications in the order of their frequency are conjunctivitis, palsies, suppurative choroiditis, and infection of any of the other structures of the eye or panophthalmitis.

Conjunctivitis is a very early complication, sometimes even occurring in the premeningitic stage. The condition is benign and usually heals spontaneously. Little treatment is necessary.

Crops of herpes on the eyelids and cornea are very occasionally seen.

Eye palsies, most often of the sixth nerve, causing strabismus, are temporary and spasmodic in character. Permanent paralyses of this nerve or of the third nerve are very rare.

Suppurative choroiditis, or infection of any of the other structures, or panophthalmitis, should be diagnosed early and the regular treatment promptly instituted. These complications, unfortunately, are quite common in meningitis, and are the most frequent causes of blindness.

The local application of antimeningitis serum here again suggests itself. The action of the antimeningitis serum following its local subdural injection has already been explained. The serum benefits principally through its local opsonic action while bathing the parts and stimulating the leukocytes to digest the bacteria. The same reaction occurs in test tubes or in injections into the peritoneal cavity of the guinea pig of live culture of the meningococcus and the specific serum. The local application of the antimeningitis serum in the eye will, therefore, suggest itself as a rational measure. In cases of conjunctivitis it certainly ought to be very beneficial. Fortunately, however, these cases clear up spontaneously and do not require any special treatment. Observations on the effect of serum locally applied should nevertheless be made. Serum used early in cases of conjunctivitis may prevent the severe complications of conjunctivitis occasionally encountered, and may possibly avert or benefit the cases with deeper infection.

The other forms of blindness are due either to pressure or nuclear lesions. Pressure is one of the rarer causes, and is seen in the forms of extreme hydrocephalus, as well illustrated in cases of posterior basic meningitis where the ventricles are markedly distended with the encapsulated exudate. A study of the fundus shows a decided blanching of the vessels, immediately followed by their filling up, with temporary improvement in vision after ventricular drainage. Other cases show a varying degree of optic neuritis.

Prognosis in cases of blindness following nuclear lesions is bad, and little or nothing can be done.

Ear Complications.—Middle-ear suppuration and deafness are the principal ear complications. Middle-ear suppuration usually remains localized, rarely extending deeper. Quite often the meningococcus can be demonstrated in the purulent discharge early in the infection. The usual treatment of paracentesis and drainage suffices.

Deafness, unfortunately, is not only one of the most dangerous, but one of the most common complications of meningitis. A small percentage of cases recover. These are probably principally caused by hydrocephalus, and with the subsidence and relief of this condition deafness clears up.

This temporary deafness is not infrequently seen during the course of chronic meningitis. The condition is relieved after each puncture and recurs as the cerebrospinal fluid reaccumulates.

Case 13.—A man, aged 47, had suffered from epidemic meningitis for 2 months. After the acute stage of the disease he had lapsed into the chronic form, the disease conforming to the milder type of chronic epidemic meningitis, hydrocephalus being the principal feature, and mild, persistent infection apparently being of less consequence. With the periodic occurrence of hydrocephalus, the patient began to complain of buzzing, roaring noises in the head and of severe deafness. With the relief of hydrocephalus by lumbar puncture, deafness promptly cleared up. After an illness of 2 months the patient had sufficiently recovered so that he could get about. He, however, complained of fairly persistent headache and considerable impairment of hearing. The pupils remained dilated and he suffered from occasional moderate diplopia. The veins of the scalp were moderately dilated; Macewen's sign was quite pronounced. The symptoms were considered to be due to hydrocephalus, and lumbar puncture was advised but declined by the patient. These symptoms persisted for a period of about 6 weeks, gradually improved, and ultimately disappeared. The patient's hearing was finally as good as ever.

Case 14.—A boy, aged 8, was admitted to the hospital suffering from a very severe acute attack of epidemic meningitis. Twenty-four hours later it was noted that he was completely deaf. Under the course of the usual active serum treatment he promptly improved and was convalescing on the tenth day after admission to the hospital. On the fourteenth day he was discharged. He was able to get about and felt well in every way; no headache; no evidence of hydrocephalus. He was absolutely deaf in both ears, however. When seen 6 months later there was no improvement. Deafness in this case was evidently due to earlier nuclear lesions.

In all cases of deafness, therefore, it is most important to determine whether or not hydrocephalus is present, since this offers practically the only hope of relief.

The other more common permanent form of deafness occurs often soon after the onset of meningitis, and is due to the destruction of the auditory apparatus. The auditory nerve, like the optic nerve, is very closely associated with the meninges. It is generally believed that the infection in the meninges extends along the arachnoid sheath of the auditory nerve into the auditory canal, spreading along the vestibular nerve and infecting the structures of the inner ear. With recovery from the primary disease the auditory nerve degenerates, and a cicatrix fills up the internal auditory canal and the structures of the internal ear. This form of deafness is independent of hydrocephalus, and is not amenable to treatment.

Joint Complications.—Under the division of complications due to general meningococcus sepsis the joint complications will first be considered. Joint involvement occurs in 15 per cent of all cases, appearing during all stages of the disease. In most instances it is a polyarthritis affecting the smaller joints of the hand and the larger joints of the upper and lower extremities. The lesion is usually benign and clears up spontaneously.

The usual acute form of arthritis occurs very early in the disease and consists of a mild, only moderately painful synovitis, which subsides without any special treatment in a very few days. Sometimes, however, the condition tends to become a chronic one, lasting weeks or months. The joints are painful and swollen, the tissues thickened, and there is moderate disability. The condition is benefited by local measures of heat, massage, and counterirritants. Meningococcus vaccine offers most hope of permanent and rapid cure. Small doses of 50,000,000 to 100,000,000 meningococci should be used at first, later followed by larger doses, until response is observed or the reaction is too severe. The doses should ordinarily be administered at intervals of from three to five days, but it is best to be guided by the response and the reaction.

A less common form of this complication met during the course of meningitis is a very severe acute arthritis. The joints are severely swollen and painful. The condition is accompanied by high septic temperature. Instead of clearing up quickly, as does the usual form, this condition tends to become more aggravated. Active radical measures are indicated. It has been found that tapping the joints and removing the fluid in them by aspiration, followed by the injection of a small dose (10 to 15 c.c.) of antimeningitis serum directly into the joint cavity, give prompt relief and sometimes brilliant recovery. Response is immediate and even more gratifying than in the subdural treatment with the antimeningitis serum. Swelling and all evidence of local inflammation usually promptly subside. This is another instance of the rational and beneficial effects under the direct, local application of specific immune sera to the infected site.

Septic Pneumonia.—Septic pneumonia is one of the more frequent terminal complications. The principal treatment is prophylactic. Delirious, stuporous patients should be turned from side to side to prevent hypostasis. The throat and mouth should be kept clean, and care should be used while feeding a patient to prevent inhalation of food.

Pyelitis.—In epidemic meningitis, as in other forms of general sepsis, pyelitis is quite common, and is evidenced not only by a bacteriuria, but also by the appearance of pus and casts in the urine. During the bacteriemic, premeningitic stage one can frequently find meningococci and pus cells in the urine in considerable numbers even before meningococci can be found in the cerebrospinal fluid. With the localization of the infection in the meninges and the appearance of meningococci in the cerebrospinal fluid, the organisms and pus cells either diminish very considerably or totally disappear from the urine. This, of course, indicates that the general infection has subsided to a marked degree. Occasionally, however, pus cells and meningococci persist in the urine, and may be accompanied by tenderness and enlargement of the kidney. This condition of pyelitis rarely, if ever, goes on to surgical kidney. It is important to recognize the condition, since sometimes one can explain persistent fever which otherwise might be attributed to the meningitis proper. No special treatment is necessary. The general measures of urotropin and active elimination suffice.

Case 15.—Boy, aged 13, after 6 days' serum treatment of epidemic meningitis was apparently making a brilliant recovery. His cerebrospinal fluid had quite cleared up; temperature had come down to normal and all clinical signs of meningitis had abated. After 24 hours of normal temperature fever again rose to 104°. The first suspicion, of course, was that the patient was suffering a relapse. He, however, presented no clinical symptoms of a relapse. A careful examination led to the discovery that the patient had a tender, slightly enlarged kidney on the right side. The urine had a moderate number of pus cells and Gram-negative diplococci which subsequently culture proved to be meningococci. Urotropin was administered in large doses. He continued to run a septic temperature, fluctuating between normal and 104° to 105° daily. In order to eliminate absolutely the possibility of a slight, persistent infection in the meninges, another lumbar puncture was done on the second day after the reappearance of these symptoms. The cerebrospinal fluid, however, was normal in every way. After a period of 10 days temperature came down to normal and with it there was a coincident clearing up of the tenderness and enlargement of the right kidney. The pus cells and bacteria disappeared from the urine.

Heart Complications.—Chronic meningococcic sepsis due to localization of the meningococcus during the period of general sepsis in any of the valves of the heart with the production of a chronic, ulcerative, or malignant endocarditis is a very rare complication. The picture is the usual one of malignant endocarditis. The cases linger from a few weeks to several months. Anemia and emaciation are progressive and infarctions more and more frequent. There is very little hope in treatment. The antimeningitis serum injected subcutaneously and active vaccination, preferably with an autogenous meningococcus vaccine, offer most hope. The antimeningitis serum should be injected at first in moderate doses of 20 to 40 c.c., repeated at intervals of a few days. If there be no response after a few doses active vaccination should be instituted, beginning at first as in other cases with small doses, repeating the doses at frequent intervals and increasing the dose until response is apparent. These cases are so rare that early diagnosis is usually missed. Active specific treatment with serum and vaccine should offer a fair percentage of recoveries if treatment be instituted early.

Serum Sickness.—While serum sickness proper is not a complication of meningitis, it is so commonly seen during the course of meningitis that it may be properly classified as one of the common complications of the disease.

The writer has noted the complication in about 60 per cent of 300 cases which he has personally observed. The antimeningitis serum is not refined or concentrated like diphtheria and tetanus antitoxin; and very large doses must be used. An average case is injected with 100 to 200 c.c. of serum during the course of the illness. Absorption of the serum into the general circulation is very rapid after its injection into the subarachnoid space; in meningitis absorption is even more rapid on account of the large area of inflammatory tissue with which the serum comes into direct contact.

Symptoms usually appear on the eighth to tenth day after the first dose of serum. Not infrequently the accelerated reaction occurs on the fourth to sixth day after the first injection in cases where the dose of serum has been repeated. The writer has also seen a number of cases where the immediate reaction occurred within a few minutes after the first dose of serum. In a few cases the history of sensitization to horse serum through previous injection with diphtheria antitoxin was obtained. In 6 cases, however, there was apparently constitutional sensitization to horse serum; no previous sensitization to horse serum had been produced. These cases conform to those which have been discussed following the first dose of diphtheria antitoxin. For reasons mentioned, however, the outlook for preventive measures with the use of this serum, is not hopeful.

The symptoms are, in the majority of cases, annoying, but not alarming, conforming in every way to the well-known picture of serum sickness and consisting of marked general giant urticaria, or a general erythema, erythema multiforme, or occasionally angioneurotic edema. There are some nausea and vomiting and moderate fever. Pain in the joints, sometimes accompanied by slight swelling, albuminuria, and general adenitis of moderate severity occasionally occurs. In the average case the patient complains of severe itching, which is very annoying and resists almost every means of treatment. It rarely lasts, however, more than from twelve to twenty-four hours.

Occasionally the symptoms above described may be much more severe and, for a time, may be very alarming, especially if the appearance of urticaria be delayed, and if there be doubt as to the causation of the symptoms. The patient may have a severe chill and develop a very high temperature; may become prostrated and sometimes may suffer severely from shock. These cases may be alarming and may even terminate in death. The following case (quoted from Sophian, *Epidemic Cerebrospinal Meningitis,* St. Louis) illustrates:

Case 16.—Moderately severe case of epidemic meningitis. Injected with serum on three consecutive days following patient's admission to the hospital, then on the fifth day, and tapped for simple removal of fluid on the seventh day. Symptoms were very much improved, child was brighter, stiffness of the neck was only slight, the Macewen was slight, temperature was 100° F., and cerebrospinal fluid had cleared up, yielding only a few intracellular organisms. On the eighth day temperature suddenly rose to 104° F. General condition was not so good. The patient vomited, appeared stupid, pulse was weak, but there were no other pressure signs. The onset of such violent symptoms in the face of previous steady improvement caused the author to suspect that possibly the meningitis was not accounting for the symptoms. General treatment was given. About 2 hours later a marked urticaria appeared all over the body. General condition became worse and pulmonary edema quickly developed. It was noticeable, however, that, while the general condition was not good, it was not as bad as it would be usually with terminal pulmonary edema. Active general treatment with cupping of the chest gave immediate response in a few hours. The following day urticaria was still present, but general condition was good and edema entirely gone.

During the course of treatment of an acute case of meningitis the development of these symptoms may be very confusing in that there may be doubt as to whether the severe general symptoms and high fever are due to a relapse of meningitis or to the serum sickness or other complications. If the patient be still suffering from meningitis, there may appear an aggravation of some of the meningeal symptoms, especially the stupor, headache and rigidity of the neck. If the patient be convalescing from meningitis, there likewise may appear a group of meningeal symptoms which may lead to the suspicion that the patient has suffered a severe relapse. Netter and Debré have described a group of cases in which severe meningeal edema was the predominating feature of the attack of serum sickness. Clinically the symptoms were very suggestive of a relapse. Lumbar puncture yielded a clear fluid with no organisms.

The appearance of the above-described untoward group of symptoms occurring on the eighth to tenth day of the disease in a patient who apparently has been doing well, and who is convalescent from meningitis, should always lead to the suspicion of serum sickness, even though the urticaria proper has not yet appeared. If the meningeal condition has been responding as well as can be expected it is well to leave the patient alone, rather than to puncture unnecessarily and further depress him.

In the writer's experience almost any secondary complication during the course of meningitis which is accompanied by fever is usually promptly attended by an aggravation of the meningeal symptoms, especially in the rigidity of the neck and Kernig's sign, even though lumbar puncture does not reveal an actual relapse or aggravation of the meningitis proper. For example, one of the writer's cases, a girl of fourteen, developed repeated crops of herpes, the last crop occurring on the eighth day of the disease when the patient was convalescing from meningitis. Each crop of herpes was attended by a rise in temperature to 104°, and each crop, furthermore, even the last, was attended by increased rigidity of the neck, stupor, and marked Kernig. It is possible that the cases described as meningeal edema complicating serum sickness might be explained in this way.

To recapitulate: On the suspicion of serum sickness it is well to leave the patient alone and treat him generally. Under no circumstances, however, should serum be administered under the impression that the patient is having a relapse if a strong suspicion points to the symptoms being due to serum sickness proper.

The great frequency of serum sickness following the injection of the antimeningitis serum should render one cautious in administering the serum by intraspinal injection if there be an interval of several days since the last dose of serum. The following instance of anaphylaxis (quoted from Sophian's *Epidemic Cerebrospinal Meningitis,* St. Louis) illustrates this danger:

Case 17.—Girl, aged 10. Moderately severe case of epidemic meningitis. Had been injected with the antimeningitis serum subdurally on 2 successive days with considerable improvement so that the attending physician thought that further serum treatment might be unnecessary. Four days later (6 days after the first dose of serum) a moderate relapse was observed and the patient was sent to the hospital. Her general condition was very good. Lumbar puncture was performed and 15 c.c. of antimeningitis serum were administered. Her condition at the end of the operation was good. Four hours later a severe, giant urticaria suddenly broke out, accompanied by delirium and symptoms of intense shock. Pulse was rapid and weak; color was cyanotic, and within an hour a severe general pulmonary edema developed. The immediate condition of meningitis was not aggravated. Active general treatment fortunately brought notable response in a few hours. The patient made an uneventful recovery from her meningitis.

The writer, in a very large experience, has never had a fatality as a result of anaphylaxis. Such fatalities, however, have been reported by other observers. Besredka, in calling attention to the great frequency of serum sickness following the use of the antimeningitis serum by intraspinous injection, mentions 10 fatal cases.

Rosanow has advised the preliminary injection of the serum subcutaneously, intramuscularly, or intravenously in doses of .4 to 2 c.c. as a protection against the anaphylaxis following the intravenous injection of serum. (The same would hold true for the intraspinal injection.)

The case quoted by Grysez and Dupuich, in which a preliminary intraspinal injection of 2 c.c. of serum given a chronic case of meningitis (the last dose of serum had been three weeks previous) did not prevent the occurrence of severe symptoms of anaphylactic shock following the injection of the therapeutic dose of serum, shows the unreliability of this method also.

Besredka goes a step farther by suggesting that a patient may be protected by the preliminary injection of repeated, instead of single, doses of serum. These should be applied at short intervals, the dose being gradually increased. This method of desensitization appears to be more effective.

Weil, in a recent publication, shows by observation on guinea pigs that the desensitizing dose varies in proportion to the initial sensitizing dose; where the sensitizing dose was small the desensitizing dose should be small and vice versa. He calls attention to the obvious difficulty of determining the necessary desensitizing dose for the human being and, therefore, the impossibility of absolutely safeguarding a patient by either the injection of a single large dose of serum or by the repeated doses. The use of the very large therapeutic doses of serum in meningitis would require very large desensitizing doses of serum injected subcutaneously.

An analysis of this subject warrants the following deductions:

Serum sickness, though of frequent occurrence following the injection of antimeningitis serum, is rarely fatal.

It is desirable to inject a protective desensitizing dose of serum if there be an interval of several days between the doses of serum.

The most practical desensitizing protective method at the present time is the subcutaneous injection of a few cubic centimeters of serum a few hours before the intraspinal dose. The complication of true anaphylaxis terminating fatally is so rare that one is not justified in withholding the therapeutic dose of serum on that account.

Treatment of Serum Sickness.—All treatment is concerned with the relief of the extreme itching and in the case of severe symptoms with general treatment for shock. The local sedatives of value are alcohol, warm sponges, sometimes ice-cold sponges, the use of bicarbonate of soda, menthol, anesthesin ointment, and other well-known local sedatives. Internally general laxatives should be taken; diet should be light. Salol and menthol appear to help, and sedatives, such as codein or, if necessary, morphin, or atropin in 1/100-gr. doses, sometimes seem to shorten the duration of the attack.

For anaphylaxis general measures of active stimulation, artificial respiration, if necessary, or chloroform for convulsions should be used.

In case of relapse serum treatment would be indicated; in case of serum sickness general treatment. If serum be injected by mistake in the latter condition the danger of "immediate" serum reaction or true anaphylaxis would complicate the existing condition. The general experience with serum treatment, however, is that neither reaction at such a time would be apt to ensue.

Relapse.—Relapse is more common than it should be with proper treatment. The principal cause is a discontinuation of serum treatment before the infection has been sufficiently controlled. One or more doses of serum injected subdurally may give such marked and prompt response that the physician is often tempted to leave well enough alone, even though the patient shows some sign of persistent infection and hydrocephalus. This combination of persistent hydrocephalus with mild infection is most dangerous, since it not only has a tendency to cause chronic meningitis, but also to invite the serious complications previously described. Thus, in many instances, cases of relapse are not relapse at all, but rather an aggravation of cases of chronic meningitis, an aggravation of the hydrocephalus and a lighting up of the infection in the meninges, which infection had only partially been destroyed. Cases such as these should properly not be classified as relapse. The patients had never really recovered.

Treatment.—The first essential in treatment is prevention. Serum treatment in cases of epidemic meningitis should be continued as long as is necessary; that is, until all trace of active infection has disappeared and all evidence of severe persistent hydrocephalus has been eliminated. If bacteria be present in the cerebrospinal fluid, and especially if they be extracellular, serum treatment should be continued.

Treatment of relapse proper should be carried out along the same lines as described for the acute condition. Indications for the doses of serum and for relief of hydrocephalus are the same as for acute meningitis. Vaccine, especially autogenous, in this condition helps more promptly to clear up the infection.

ANALYSIS OF INFLUENCES AFFECTING PROGNOSIS

Prognosis of all infections depends upon the same factors: (1) the severity of the infection; (2) the resistance of the patient; and (3) the character of the treatment employed.

The mortality rate (70 to 90 per cent) of cases not treated with serum speaks for the severity of the infection in meningitis. The fulminating, severe bacteriemic cases offer the worst prognosis. These often die before any treatment can be instituted. The average acute case offers best hope of response to serum therapy if treatment be instituted within two to three days after the onset of the disease. The prognosis of the chronic meningitis cases is much worse; many more die, and those recovering often have serious sequelæ.

The prognosis of the posterior basic meningitis cases is uniformly bad.

The most important factors in the resistance of the patient are the age and general condition of health. Age incidence is an important influence, most probably on account of the ability to resist infection. Prognosis in children under one year of age is very bad. Fully 50 per cent die, even with early instituted specific serum treatment. Likewise the prognosis in old people is not so good. Robust individuals in good health have, of course, a better prognosis than weak individuals. The prognosis is especially poor among alcoholics, who have a tendency to develop violent, exhausting delirium and early hypostatic pneumonia.

Table of Age Mortality *

Age	Reported by			
	Flexner (Per Cent)	Netter (Per Cent)	Dopter (Per Cent)	Author (Per Cent)
Under 1 year	50.0	50.0	48.6	50.0
1 to 2 years	42.1	0.0	20.1	21.2
2 to 5 years	23.5	16.6	9.3	17.5
5 to 10 years	11.4	12.5	8.5	9.0
10 to 20 years	23.8	0.0	10.2	18.0
Above 20 years	26.4	0.0	14.1	32.0

* From Sophian's Epidemic Cerebrospinal Meningitis, St. Louis.

The most important influence affecting prognosis in meningitis is treatment. Treatment in turn is most influenced by the early diagnosis, the use of a potent, highly immune serum, the proper administration of serum, and the active administration of treatment until the infection is thoroughly under control. Early diagnosis is most important. Statistics recorded by all authors under the best form of serum treatment confirm that the most successful results are obtained when treatment is begun on the first to third day of the disease; next best, when treatment is begun on the fourth to the seventh day of the disease, and worst results when treatment is instituted later in the disease. The table on page 52 graphically bears this out.

The importance of a highly potent antimeningitis serum is apparent. Unfortunately there is no accurate method of standardizing the antimen-

MORTALITY PER CENT *

Day of the Disease When Treatment Was Begun	Flexner's Cases (712)	Dopter's Cases (402)	Netter and Debré's Cases (99)	Author's Cases (180)	Author's Corrected Statistic Cases (161)
First to third day........	25.3	8.20	20.9	13.0	9.0
Fourth to seventh day.....	27.8	14.40	33.3	23.6	14.9
Later than seventh day....	42.1	24.10	26.0	37.1	22.6
Average mortality	34.1	16.44	28.0	25.0	15.5

* From Sophian's Epidemic Cerebrospinal Meningitis, St. Louis.

ingitis serum. The standard for diphtheritic and tetanus antitoxins is uniform so that the federal government can check up the products offered on the market and prove whether or not a product contains the required number of immune units. The methods used in determining the potency of a serum, consisting of the opsonic test, bactericidal test, complement-fixation test, all depend, to a very great extent, upon the personal equation and the reagents used in the test so that a uniform standard in terms of opsonic units or complement-fixation cannot be established. Variations and fluctuations in potency of different preparations of the antimeningitis serum can, therefore, be readily understood. This, without a doubt, explains some of the poor results recorded at different times in treatment. All manufacturers of antimeningitis serum should carefully check up the potency of their product, not only by laboratory biological tests, but by carefully watching the results of clinical tests as well, since by the latter observations alone can one be absolutely certain whether or not a product is up to the desired potency.

The importance of properly administering the antimeningitis serum has been fully explained in the preceding pages. It must always be borne in mind that incorrect technic may be both harmful and very dangerous—harmful in that the patient is temporarily depressed after the injection of the serum, allowing the infection to gain headway temporarily, and dangerous in that the patient may be killed as a direct result of improper injection. The patient should always be carefully watched during the operation, and blood-pressure observations should always be made.

The importance of properly following up the serum treatment is now also apparent. Dangerous chronic forms of meningitis and posterior basic meningitis will, to a very marked degree, be prevented, and many of the dangerous complications and sequelæ will be avoided. Treatment must always be actively kept up as long as bacteria persist in the cerebrospinal fluid in any numbers, the exception to this being where there is a prompt response under serum treatment and a few intracellular bacteria persist in the cerebrospinal fluid. With accompanying good clinical condition one is in these cases warranted in waiting twenty-four hours, or possibly a little longer, before treatment is again administered.

Subjective and objective symptoms of hydrocephalus must also be carefully watched, and, if persistent, hydrocephalus must be treated by simple puncture with removal of fluid. Cases of posterior basic meningitis should be recognized early and direct intraventricular puncture be performed at the earliest moment. This is the only possible hope for these cases, and active intraventricular treatment should in all cases be instituted and kept up as long as there is any hope.

It has been demonstrated by the writer and others that the meningococcus is made up of a number of strains, as differentiated by immune serum tests. This difference in strains explains why some writers believed that posterior basic meningitis was produced by an organism differing from the meningococcus, and also explained such classification as the parameningococcus.

It is very probable that an epidemic in a community is produced by the same strain of meningococcus. Occasionally some cases of only moderate severity resist the serum treatment, even though it be instituted early and under favorable conditions. Such failure can be explained by the causation of the disease by a strain not included in the immune antimeningitis serum employed.

The most valuable signs of response to serum treatment are the effect upon the sepsis and clearing up of the hydrocephalus. The effect upon the fever is especially striking. About one-third of the cases show favorable response by critical fall in temperature, and many others by gradual fall to normal by lysis a few days after serum treatment is begun.

Prompt improvement and rapid clearing up of violent delirium, stupor, and convulsions are likewise very remarkable. A not uncommon picture is a violently delirious, restless, noisy patient one day and, twenty-four hours later, after serum treatment, a rational, quiet, sleeping patient.

General improvement and clearing up of active signs of meningeal inflammation, as evidenced by improvement in the Kernig sign and neck rigidity, often go hand in hand with clearing up of the active mental symptoms.

The most convincing sign of improvement, however, is demonstrated by microscopic examination of the cerebrospinal fluid. The change in the sediment after one dose of serum from the picture of many bacteria, mostly extracellular, to a microscopic picture twenty-four hours later of few bacteria mostly intracellular, is absolutely convincing. As a rule there is coincident macroscopic evidence of improvement in the clearing up of the turbid cerebrospinal fluid. This alone, however, is often misleading. At times the cerebrospinal fluid becomes much more turbid after a dose of serum, even with marked improvement. This may be explained by referring to the action of the antimeningitis serum. The serum acts principally through its local stimulation of leukocytosis and phagocytosis. Thus sometimes the fluid becomes more turbid on account of increase in polymorphonuclear leukocytes, but microscopic examination shows few bacteria, and those intracellular.

Improvement in hydrocephalus, as has been explained, is not ordinarily as prompt as the subsidence of the infection. A rapid clearing up of hydrocephalus, as shown by the diminution in the quantity of the cerebrospinal fluid obtained by lumbar puncture, is especially gratifying. We must reiterate, however, that total diminution in quantity of fluid alone does not mean improvement, since sometimes symptoms of sepsis are much aggravated, even though the quantity of exudate be less. The possible onset of posterior basic meningitis indicated by the small quantity of fluid obtained by lumbar puncture must always be borne in mind.

The most important immediate effect of proper serum treatment is in shortening the period of the illness and in the effect on prognosis. Before the days of serum treatment the disease was either rapidly fatal or long drawn out, and finally fatal in the majority of cases. The few cases of recovery rarely lasted less than one week. Fully 50 per cent were drawn out over five weeks or longer. As a significant contrast is the recovery of most cases in the short period of from one to two weeks, many cases clearing up absolutely in from five to six days after the beginning of treatment.

The comparison of mortality statistics in cases treated without serum and those treated with serum is very interesting. The writer's personal experience in the Texas epidemic of 1912 is very significant. During the months preceding his arrival in Texas there were about 105 cases in Dallas and the immediately surrounding country. The mortality among these cases was fully 90 per cent. Some of the few reported cases of recovery were later treated by the writer for relapse, chronic hydrocephalus, posterior basic meningitis, and other complications. On account of the previous scarcity of serum most of the 105 cases had not had the benefit of full serum treatment. A large proportion of those who had been treated with serum had not had the advantage of repeated injections. During the months following his call to Dallas the writer treated personally 180 cases with a gross mortality rate of about 16 per cent. Dr. Steiner, President of the State Board of Health of Texas, collected during this epidemic a total of 2,280 cases in the state. The mortality among the serum-treated cases was 37 per cent as against a mortality of 77 per cent among those not treated with serum. Complications among the recovered serum-treated cases were relatively few as against the complications among the recovered who were not treated with serum. This reversal of mortality statistics has been the experience throughout the world since the introduction of the antimeningitis serum. In the New York City epidemic of 1904-1905 the mortality was 90 per cent among 2,000 cases. In 1906 among 1,032 cases reported during the height of the epidemic 812 died—a mortality of 78.7 per cent. In 1907 among 828 reported cases there were 642 deaths—a total mortality of 77.5 per cent. The following tabulation of a few of the reported statistics bears out this remarkable reversal in figures since the introduction of serum treatment:

Reported by	Cases Treated with Serum		Cases Treated without Serum, Percentage Mortality
	Number	Percentage Mortality	
Flexner	1,400	31.4	70-80.0
Steiner	2,280	37.0	77.0
Netter	100	28.0	49.0
Dopter	402	16.44	52.14
Levy	165	18.18	65.0
Sophian	161	15.5	....

PROPHYLAXIS OF EPIDEMIC MENINGITIS

Epidemic meningitis is caused by the meningococcus. The disease primarily begins as an infection of the nasopharynx by the meningococcus. The organism can be demonstrated in the secretion of the nose and throat in 90 per cent of the stricken during the first ten days of the illness. During epidemics a large percentage of healthy contacts become infected with the organism and harbor the meningococcus in their noses and throats. The great majority, however, fully 95 per cent, of such contacts—healthy carriers—do not suffer otherwise from the presence of the meningococcus in their noses and throats, except possibly to develop a slight nasopharyngitis. During epidemics as many as 55 per cent of all healthy individuals exposed to the disease become healthy meningococcus carriers. The organism may remain in the nose of these carriers for a very short time and disappear spontaneously. It may disappear for a short time and then recur at intervals or may persist for a very long time—months or even years.

Healthy meningococcus carriers are the serious menace during epidemics, and are the immediate cause of the spread of epidemics. The carriers propagate the organism, producing other carriers, a small percentage of whom develop the disease. In addition these carriers are always in constant danger of developing the disease themselves, should their resistance be lowered.

Prophylactic measures against epidemic meningitis must be concerned with: (1) measures of quarantine against carriers both among the ill and healthy so as to prevent the further dissemination of the organism; (2) employment of measures to destroy the organism in the nose and throat of known carriers; and (3) employment of specific measures (such as are used against typhoid fever) to produce immunity among as many healthy individuals as possible in an infected community, of course, preferring individuals who have been exposed to the disease.

QUARANTINE

All prophylactic measures, especially quarantine, are really only indicated during epidemics. The presence of sporadic cases alone does not warrant using severe prophylactic measures.

All cases of epidemic meningitis must be strictly quarantined. Quarantine should only be raised when the patient has recovered and when two or more cultures of the nose and throat have confirmed the disappearance of the meningococcus.

The nurse and other attendants of those ill should use the same precaution as in treating other contagious diseases. The sick-room gown should be worn, and, where there is close contact with the disease, a gauze face mask. Special care must be taken that the patient does not cough in one's face. All attendants should employ the general prophylactic measures which will be described in the succeeding pages.

All discharges from the nose and throat of the patient must be carefully destroyed. Likewise all excreta, especially the urine, should be thoroughly disinfected and the dressings used in the treatment of complicating infections of the eye, the ear, the secretion of herpes should be immediately destroyed.

All healthy members of a family in which meningitis has occurred should be quarantined on suspicion until a culture of the nose and throat is taken. Positive culture demonstrating the meningococcus indicates close quarantine with the use of local antiseptic measures for the nose and throat. Quarantine should only be raised when the cultures of the nose and throat on two successive occasions prove negative. During severe epidemics close contacts, even though their nose and throat cultures prove negative, should be quarantined arbitrarily for a period of at least a week, during which time they should use antiseptic sprays for the nose and throat.

The measures of strict quarantine controlled by cultural studies are just as practicable and possible in epidemics of meningitis as in epidemics of diphtheria. That it is feasible and possible has been proved in the control of small institutional outbreaks, and especially well demonstrated in the Texas epidemic of 1912. The writer at that time, with the support of the civil authorities, was able to introduce strict measures of quarantine. Wherever possible all cases of meningitis were removed to a special meningitis hospital. All homes in which meningitis occurred were immediately quarantined. Close contacts were arbitrarily segregated for at least a week, even if cultural studies of the nose and throat proved negative. Coöperation among those quarantined was readily offered in almost all instances.

A central laboratory was established from which a number of assistants went out daily to the quarantined homes (families in which cases of meningitis occurred). The assistants carried swabs and cultural material for smears of the noses and throats. Fairly accurate reports could be made within twenty-four hours. A very simple method is to use ordinary throat culture swabs and Loeffler's tubes of culture media. After the tubes are inoculated they are incubated at 37° C. for eighteen to twenty-four hours. Smears are then made from the surface growth and stained with Gram's stain. If Gram-negative diplococci be found a tentative positive report is given, while further cultural studies are made to identify the Gram-negative organism so as to prove whether it be the meningococcus or one of the other members of the Gram-negative group of cocci. The growth is inoculated on several other slants after first carrying through several water blanks. If the meningococcus be present, typical discrete colonies usually develop within eighteen to twenty-four hours which can almost be absolutely identified by morphology alone.

During the Dallas epidemic a great many healthy contacts were quarantined in this way. They were informed that they were positive carriers so that they could immediately use prophylactic measures in the form of sprays and prophylactic specific treatment; they thus not only protected themselves in destroying the meningococcus in their nasopharyngeal secretions, but at the same time protected the community. It is true that not all carriers can be isolated during an epidemic. Each positive carrier, however, is a severe menace, and every one who is quarantined and prevented from further spreading the infection helps considerably in stamping out the epidemic.

In Dallas quarantine was controlled in this way in many families. After a period of quarantine lasting about a week cultures of the noses and throats were again taken. If negative on two successive occasions quarantine was lifted.

The community in general was warned of the nature of the infection and advised not to congregate in crowds, to keep the homes properly ventilated and clean, and to guard against promiscuous spitting. Schools were temporarily closed. People were especially warned to be careful to prevent attacks of common cold.

During epidemics cases of multiple infection are much more common than supposed. Strict measures of quarantine immediately with the simultaneous application of general prophylactic measures undoubtedly help to reduce the number of these multiple infections.

Medicinal treatment in the form of sprays, local applications, and internal medication employed as prophylactic measures are especially indicated among exposed people, and more especially for known healthy carriers. These expedients, however, should also be employed by all members of a community where an epidemic is raging.

Local treatment of the nose and throat of known and unknown carriers should be in the nature of mild, cleansing douches and mild antiseptics. Care should be taken to select an antiseptic that is not irritating. Irritating antiseptics by inflaming the tissues only predispose more to the infection. In the writer's experience the simple, mild, non-irritating treatment, consisting of mild saline douches, three times a day at six-hour intervals, followed by spraying with weak peroxid solution (½ to 1 per cent), is very efficient. Positive carriers after such treatment became negative in a very few days. A number of controls without such treatment, when examined after a week, still harbored the organism, whereas the meningococcus could no longer be found in the secretions of those treated. Other antiseptics may be employed and are useful. Some have recommended argyrol, protargol, chlorin water, menthol, and pyocyanase. The writer found that hydrogen peroxid preceded by salt solution gave the most rapid results. Other observers, however, found that the antimeningitis serum used as a spray gave the quickest results. One of the principal objections to the use of the antimeningitis serum undiluted is that the antimeningitis serum usually marketed contains a strong preservative varying from 0.2 to 0.4 per cent tricresol, which is very irritating to the mucous membrane of the nose and throat.

In the French army regular routine treatment for the nose and throat is used by all members of a garrison in which the disease has occurred. The throat is swabbed regularly with 3 per cent iodin, followed by gargling with peroxid of hydrogen. In addition an inhalation mixture is recommended. The preparation suggested by Vincent and Bellot follows:

Iodin	12 gm.
Guaiacol	2 gm.
Thymol	35 cgm.
Alcohol, 60 per cent	200 gm.

This form of treatment is rather rigorous and unnecessary. The milder treatment of saline douche and peroxid spray suffices and is unobjectionable. The severer treatment used by some, and in the French army, is so objectionable that probably most often it is not done carefully and missed by the men so that the purpose is altogether defeated.

Urotropin, on account of its antiseptic properties and its elimination through the nasal mucosa and through the urine, and its excretion into the cerebrospinal fluid, naturally suggests itself as a suitable prophylactic against the disease, and one that might be generally used among healthy individuals. The writer suggested the use of this drug in the 1912 epidemic in the Southwest. It was employed very extensively. It was very difficult, however, to make observations on the possible efficacy of this drug alone, since in almost every instance where it was used other local measures such as sprays and douches were also employed. Flexner, in his experimental work, found that the preliminary administration of the drug in monkeys afforded them some protection later against the injection of poliomyelitis virus experimentally injected. This, too, points to the possible efficacy of the drug.

Specific Prophylactic Measures

The trend of all modern therapy of infectious disease is toward the elaboration of specific measures which will directly influence and counteract the infectious agent. In treating infectious disease sera and antitoxins have been used to neutralize and destroy the infection—well illustrated in the use of diphtheria antitoxin in diphtheria, the therapeutic use of the antimeningitis serum, tetanus antitoxin, streptococcic sera, and other immune sera.

The purpose of vaccines in treating disease is to stimulate the patient to produce immune bodies in larger quantities than he has himself been able to generate. Thus we see the successful therapeutic use of staphylococcus vaccine, acne vaccine, and other vaccines.

Sera and vaccines have likewise been used to prevent disease. The injection of an immune serum into a person exposed to a disease for which the serum is specific will give him immediately a quantity of immune bodies with which to combat the infection. This period of protection, however, only lasts as long as these immune bodies persist in the system. They are usually eliminated within a few weeks—as a rule within two to three weeks. Diphtheria antitoxin is perhaps the best illustration of an immune serum frequently used to combat disease. Its use among exposed members of families where diphtheria has occurred has prevented in most instances the appearance of multiple infections of diphtheria. Likewise tetanus antitoxin, when used in sufficient doses, affords almost complete protection against tetanus during the period that the antitoxin remains in the system. As a rule this temporary protection of from two to three weeks suffices, since the infectious agent very often lodged in the healthy tissues frequently disappears or dies out during this period of protection. Sometimes, however, it persists in the tissues and may cause disease later.

Permanent protection can be produced by the use of vaccine. The patient is stimulated to produce his own immune bodies which remain in the system for very long periods, often for years. The advantage of sera over vaccines lies in the fact that the former produce immediate immunity and give the patient protection at once, whereas the latter require at least the period of a week after the first injection before any appreciable immunity occurs. Then, too, immediately after the injection of a vaccine a negative phase may occur, during which period the patient's resistance is lowered so that there is added temporary danger of the disease occurring if the infectious agent be present in the tissues. The dangers of the negative phase can to a very great extent be eliminated by proper precautions, particularly as to dose and in the use of other prophylactic measures that will be described later.

The best known and most successful example of vaccination against disease is the use of typhoid vaccine. Typhoid fever—a dreaded garrison disease—has been almost entirely eliminated in armies where typhoid vaccine has been properly employed. Similarly the use of typhoid vaccine in civil communities and in hospitals has very materially reduced the occurrence of the disease.

The great boon in the establishment of successful specific prophylactic measures against as dangerous a disease as meningitis is apparent. During epidemics work in whole communities is very often paralyzed. The spread of the disease through the medium of healthy carriers, the great uncertainty as to whom the disease will next affect, are sources of great anxiety. Reliable, specific, prophylactic treatment would be most gratefully welcomed by everybody.

A moderate dose of antimeningitis serum injected subcutaneously undoubtedly affords considerable protection against the disease for a few weeks. During the Texas epidemic the writer advocated the widespread use of this expedient, especially in communities where multiple infections were common. Doses of 10 to 15 c.c. were recommended. The measure was used principally among close contacts. No case of secondary infection occurred in those who had been so protected during the period in which protection would be expected; that is, from two to three weeks after the dose. One individual, a porter at the Meningitis Hospital, developed meningitis about six weeks after he had been injected. The great objection to the measure is the fact that protection is only afforded for a few weeks after a single dose, and the fact that the injection of so large a dose of unrefined serum is commonly followed by an attack of serum sickness which, to say the least, is extremely annoying. Individuals so injected are also in danger of developing anaphylactic shock should they subsequently require an injection of horse serum whether it be for a subsequent attack of meningitis or for use in other disease, as diphtheria, tetanus, or other infection.

The danger of serum sickness may be eliminated to a marked degree by reducing the dose of the serum. The writer is now inclined to believe that a dose of 5 c.c. of the usual unrefined serum will afford ample protection against the disease. Even a greater reduction in the dose can be made by using a refined serum so that the relative immune units are still retained. The writer is now making observations on this subject to determine the relative potency of a concentrated serum.

The danger of anaphylaxis is a more important one, especially if the patient should subsequently develop meningitis and require the therapeutic use of serum immediately. In such an event the patient should first be injected with 1 to 2 c.c. of serum subcutaneously. If the patient does not react, or even if he does react, a larger therapeutic dose of serum can be injected within a few hours with less danger of developing anaphylaxis (see discussion under Serum Sickness).

The field of prophylactic serum vaccination against meningitis has not been studied sufficiently. Extensive observations will undoubtedly afford very interesting data.

Prophylactic meningococcus vaccination against meningitis naturally seems the most direct method of protecting a community over a long period of time. Clinical and laboratory studies of epidemic meningitis yield data that are favorable to the application of this measure. Epidemic meningitis is a bacterial disease. One attack with recovery affords almost complete protection against the disease. Immune bodies can be readily demonstrated in the blood during the course of the disease. Agglutinins and opsonins have been demonstrated in quite high dilution during the disease and precipitins and complement-fixation bodies have similarly been found, though in smaller quantities. Immune bodies have been demonstrated in the blood of those recovering from epidemic meningitis through the use of the blood serum of recovered cases in treating those acutely ill with epidemic meningitis. In a few cases the blood serum so used by intraspinal injection gave fair results. Similarly all of the above-mentioned immune bodies have been demonstrated in the cerebrospinal fluid of meningitis cases, though, of course, in very small quantities.

Likewise immunity studies on small and large animals have proved that very high immunity can be produced by vaccination with increasing doses of dead and live meningococci. A very simple experiment is the injection of rabbits with killed meningococci. A few doses of vaccine will enable one to protect the rabbit against a larger lethal dose of culture.. The use of goats, sheep, monkeys, and horses for the production of a highly immune antimeningitis serum which has been used so successfully in treating the disease in human beings has enabled more accurate and thorough studies of such sera with the demonstration of immune bodies of all orders in very high dilution.

Influenced by these facts, the writer felt justified in advocating the use of prophylactic vaccination during the height of the 1912 Texas epidemic, since the disease was spreading in spite of all measures employed. He recommended doses of 500,000,000, 1,000,000,000, and a third dose of 1,000,000,000 at weekly intervals. Relatively very little discomfort, no more than that following typhoid vaccination, was experienced after the injections. Several hundred people were injected within a period of about six weeks. Almost all who were vaccinated had been exposed to the disease, many being doctors and nurses who were in constant touch with the sick. None of those who were fully vaccinated with three doses developed the disease. One nurse and a physician contracted meningitis after incomplete vaccination, two doses only having been given. In both instances the disease was mild and recovery prompt. Eleven other nurses who were not vaccinated developed meningitis, the disease being very severe in some instances.

Toward the end of the epidemic the writer was able, with the assistance of Dr. Black, of the Southwestern Medical College, to undertake experimental observations on the effect of vaccination with varying doses of meningococcus vaccine. Eleven medical students volunteered for the study. The students were divided into two squads. The members of one squad were injected with 500,000,000 killed meningococci as the first dose, and 1,000,000,000 as the second. The others were injected with 1,000,000,000 killed meningococci as the first dose, and 2,000,000,000 as the second. Injections were made at seven-day intervals. Some of the members of the first group received a third injection of 1,000,000,000 killed meningococci, and some members of the second group were injected with 2,000,000,000 killed meningococci. Observations were made on the local and general reaction and on the blood picture.

The vaccine was prepared from a strain of meningococcus which had been isolated from a case of meningitis in Dallas. The vaccine was prepared as follows: The organism was grown on glucose agar from eighteen to twenty-four hours, then washed off in salt solution, shaken thoroughly, standardized, and killed by heat in a water bath at 50° C. for one hour.

A slight leukocytosis occurred in practically all students after the injection, the blood picture returning to the normal on the third to fourth day. There was little change in the total differential blood count. On the whole the blood smear and count showed negligible changes.

Studies of Immune Body Content in Blood of Vaccinated.—About ½ c.c. of blood was obtained from the finger of the vaccinated and collected in sterile glass ampules every four days. After clotting, the tube was centrifuged and the serum separated. Suitable dilutions were then made in salt solution and examinations made for the presence of immune bodies, agglutinins, and complement-fixation in the blood.

Agglutinins developed rapidly in all the vaccinated as early as four days after the first dose, good agglutination being obtained in dilutions of 1:20 to 1:60. After the second dose most of the sera agglutinated in dilutions of 1:100 to 1:500 a few days after the injection. The examinations a week later where no further injections were given showed an increase in the agglutinating power of the serum up to 1:1,000 to 1:500. The greatest response occurred in the students who were injected three times. There was relatively little difference in the degree of agglutination in the sera of those who were injected with the smaller doses as compared with those who were injected with the larger.

Complement-fixation studies showed an increase in the third order of immune bodies in very much the same ratio as in the case of the agglutinins, though the total increase in quantity of these immune bodies was not as high as in the agglutinins. At the end of the third week some of the sera showed fixation in dilutions of 1:200 of the sera, this being a very high degree of fixation. As in the case of the agglutinins, so here there was relatively very little difference in the response as to the formation of immune bodies after the larger doses in the one group as compared with the smaller doses in the other group.

Clinical Reaction after Injection of Vaccine.—The local reaction is very much the same as after injection of other vaccines, notably the injection of typhoid vaccine. A few hours after injection there are redness, swelling, and tenderness at the point of inoculation. Some subjects react much more severely than others. Pain in any marked degree rarely lasts longer than twenty-four hours. One would expect the later injections to be more painful than the initial. In some instances this is true, but in the writer's experience the later injections, even though they be in greater doses, are followed by much less reaction.

General constitutional symptoms are frequently missing. Most often the patient complains of moderate headache and general malaise. Occasionally there is a rise in temperature of 1° to 3°. Sometimes, however, there is a marked rise in temperature to 104° or even 105° F. The patient may suffer from nausea, have general bodily pain and vomit. Labial herpes develop in some cases.

Sometimes an alarming group of symptoms occurs. About eight hours after the injection the patient may complain of severe headache, have rigors, vomit, and complain of pain in the nape of the neck. After a few hours the symptoms improve and then entirely disappear within a very short period. These symptoms are particularly alarming on account of the pain referred to the nape of the neck and the suspicious symptoms of meningitis. Even a superficial examination, however, will readily exclude the true disease. All of the other active signs of meningitis are missing. The patient is, as a rule, not acutely ill, improves very rapidly, and has absolutely clear mentality. This symptom-complex is most apt to occur after initial large doses. The condition can probably be explained by the nature of the meningococcus and its effect upon the human being. The probable occurrence of meningitis as a complication of the initial meningococcus sepsis can best be explained by the special affinity of the meningococcus and its toxic product for the meninges. After there have been sufficient depression and irritation by these toxic products then the meningococcus proper can localize in the meninges and set up the true infection. If this theory be true, one can then explain the occurrence of the peculiar symptoms after the injection of a large dose of meningococcic vaccine. The soluble products of the dead meningococci irritate the meninges the same as do the solution products of the live organism, though, of course, to a much less degree. This, then, explains the clinical symptoms suggestive of mild meningeal irritation.

As a result of this experience the writer has advocated the use of a smaller initial dose of vaccine, and now recommends an initial dose not over 100,000,000 killed meningococci.

Analysis of Vaccination Studies.—A study of the observations on the vaccinated students demonstrated that a vaccine properly prepared and injected in adequate doses stimulates a prompt response in the formation of immune bodies immediately after the vaccination. The group of students who were vaccinated with the smaller doses formed immune bodies in almost as large quantities as those who were injected with the very large doses. The local reaction is very much the same as after other bacterial vaccines. Occasionally a subsequent dose of vaccine will result in the formation of an abscess in which some of the dead meningococci may be found. The general reaction in most instances is also the same as after the use of other vaccines. After the employment of very large initial doses there sometimes occurs a group of symptoms which, while not serious, may be alarming to the inexperienced. The symptoms of suggestive meningitic inflammation subside very promptly—within a few hours. The writer has not been able to demonstrate the occurrence of a negative phase by examination of the blood. It is now recognized that the so-called negative phase is a very much exaggerated condition, provided, of course, that ordinary everyday precautions of using suitable, not excessive, doses are observed. Among the several hundred clinically vaccinated during the Dallas epidemic almost all had been intimately exposed to the disease. No cases of meningitis followed the use of vaccine, even though meningococci could be demonstrated in the nasal secretions of some of the vaccinated. The data of several hundred vaccinated during the Dallas epidemic were, of course, far from conclusive. The fact, however, that many multiple cases were occurring during the epidemic, and that no case occurred among those who had been fully vaccinated, even though many of the vaccinated were most intimately exposed to the disease, must be of some significance. The occurrence of two cases in a physician and a nurse who had been incompletely vaccinated sounds the same warning as did the apparent failure during the first year of typhoid vaccination. One must be most careful to select a vaccine which is potent. If possible, a strain of meningococcus that has been demonstrated to stimulate the production of immune bodies in large quantities should be used. Furthermore, the vaccine must not be overheated. A temperature of 50° C. suffices to kill the meningococci. Preservatives must not be added in excessive quantities. If good, careful technic be used in the preparation of the vaccine a very minute quantity of preservative (0.1 per cent tricresol) will suffice. The desirability of examining the blood of the vaccinated to actually determine whether or not immune bodies have been produced is apparent.

Encouraged by these observations, the writer determined to study further the effect of vaccination, and to note the duration of immunity after vaccination and to follow the clinical course of as many vaccinated subjects as possible in order to ascertain whether protection was afforded, especially where the vaccinated were intimately exposed to the disease during epidemics. During the following year, 1913, Texas had a moderate amount of meningitis, though it was really free from an epidemic. Vaccine was used in quite a considerable number of people; it was employed both in civil communities and in institutions. The writer had no way of definitely finding out the number of people vaccinated. As far as he could judge there were at least 5,000. He could find no record of meningitis developing among those vaccinated. He was personally able to follow the vaccinations among 300 people in his immediate city. Most, or all, of the vaccinations were in families in which the disease had occurred. In no instance was there a case of multiple infection. Prophylactic vaccine against meningitis was exploited during the year 1913 by a number of manufacturers of biologic products. The measure, therefore, was used in moderate quantities all over the country. In 1913 quite severe epidemics occurred in Tennessee, Arkansas, and Nebraska. Prophylactic vaccination was liberally employed in these communities. As far as can be learned from reports, the vaccinations appeared to be successful.

Undoubtedly the clinical observations must definitely establish the status of this measure. Observations must be made in many thousands of cases before any positive deductions are warranted. The clinical data so far, however, are encouraging.

The writer examined the blood sera of 6 people whom he had personally vaccinated a year and a half previously, and demonstrated by the complement-fixation test immune bodies in all. Two of the vaccinated had been injected with but two doses of vaccine, 100,000,000 and 500,000,000 killed meningococci respectively; the others had been injected with 100,000,000, 500,000,000, and 1,000,000,000 killed meningococci at seven-day intervals. In all there was equally good complement fixation of the serum in 1:100 dilution.

Wherever possible, the blood serum of the vaccinated should be examined about a week after the last dose of vaccine. The simplest method is the complement fixation test. The following technic is suggested: Prepare a suitable antigen by growing the meningococcus on glucose agar for from eighteen to twenty-four hours. Wash off the growth in salt solution, heat at 50° C. for two hours, then allow to autolyze from twelve to twenty-four hours. It may then be filtered or used direct. The antigen will usually be potent for a few days. After that, however, it will become anticomplementary. A more stable antigen may be prepared according to the method suggested by McNeil of the New York Research Laboratories. This consists of growing the culture in salt-free agar, washing off the growth in distilled water, and heating at 50° C. for three hours, then immediately filtering through a Berkefeld filter. The clear filtrate is stable for longer periods, from a few weeks to a few months.

It is desirable to make an antigen from a number of different strains, since it has been proved that the meningococcus family, like other organisms, is made up of many strains of the organism. One should, therefore, include in the antigen as many strains as possible. The selection of different strains, however, can only be made by differentiating the strains after examining a great many organisms by laboratory serological methods. This differentiation is rather difficult, and the rough, cruder method of simply selecting a number of different organisms isolated from different cases usually suffices.

The other materials in the test are the same as for any complement-fixation test done according to the Wassermann method. The patient's blood serum should be obtained. A simple method is to collect the blood in a capillary pipet, 0.25 to 0.5 c.c. of serum sufficing. The Wassermann sheep hemolytic system is a convenient method, though the Noguchi method is just as good. In using the Wassermann system the writer, following McNeil's suggestion, has been using one-tenth the bulk of the whole test, using, therefore, in proportion, instead of one-tenth of the patient's serum, one-hundredth; instead of 1 c.c. of corpuscles, 0.1 c.c.; instead of 0.1 c.c. of complement, 0.1 c.c. of a 10 per cent solution complement, and so on. The technic is simple. The antigen should first be titrated to determine the degree of dilution necessary to eliminate anticomplementary action, and at the same time retain strong binding power, as proved by testing with a known positive serum.

A test of this kind is not concerned with the quantitative findings, but rather with the determination as to whether immune bodies are present. Therefore, the writer has been accustomed to use simply 1:100 and 2:100 c.c. of serum (corresponding to the 0.1 and 0.2 for the full Wassermann test). The antigen and complement in suitable quantities should be added and incubated for one-half hour, then the corpuscles and the antisheep amboceptor added, and in turn incubated for one hour. Of course negative and positive controls are employed in every test. Readings are then made. Positive reaction is obtained in most instances after full vaccination. Failure to obtain positive vaccination should make one inquire into the preparation of the vaccine used, especially as to the temperature employed in killing the meningococci, and to look for possible idiosyncrasy on the part of the patient.

This technic is essentially the same as is now commonly used for the diagnosis of gonococcic infection by the complement-fixation test. Any well-equipped laboratory should be able to do the test at only a moderate cost to the patient.

The writer has not been able in his subsequent studies to determine any great danger from the negative phase. He was especially impressed, however, with the desirability of beginning with an initial small dose, preferably not over 100,000,000 killed meningococci. It is often quite difficult to obtain a coincident examination of the secretions of the nose and throat before vaccination. In about a dozen instances the writer has found meningococci in these secretions at the time of vaccination. These cases showed no greater reaction than the others vaccinated. In a few instances where opportunity was afforded for a subsequent examination of the nasal secretion—from one to two weeks after the vaccination—the organism had apparently disappeared, though no local treatment had been employed. As an extra precaution, however, it might be well to suggest local treatment of sprays and nasal douches for the first week of the vaccination period. Where the vaccinated subject has been very intimately exposed to the disease it would be well as an added precaution to first take cultures of the nose and throat. If positive it would be safer to use sprays for the nose and throat and to take urotropin internally for a few days.

Experience with prophylactic vaccination so far undoubtedly warrants further study. Observations should be made coincidentally by the clinician and the laboratory worker, and in all instances, if possible, a vaccine properly prepared should be used. The special precautions in the preparation of a vaccine are the selection of a suitable strain which will stimulate the production of immune bodies in the persons vaccinated and care not to heat the vaccine over 50° C. A minimum amount of preservative should be used.

In the order of their importance prophylactic measures against epidemic meningitis may be summarized as follows:

Quarantine of all sick and as many known healthy carriers as possible. Arbitrary quarantine should be enforced for a period of at least a week or ten days. Wherever possible the period of quarantine should be determined by cultural examination of the nasopharyngeal secretion, raising quarantine only when cultures of the nose and throat have been proved negative for the meningococcus.

The use of mild antiseptic sprays for the nose and throat, one of the simplest being a spray of ½ to 1 per cent peroxid of hydrogen.

The use of urotropin internally in doses of 25 to 35 gr. daily.

Prophylactic meningococcic vaccination. Three doses are desirable, beginning with a small dose of 100,000,000, the later doses being 500,000,000 and 1,000,000,000 of killed meningococci respectively injected at weekly or ten-day intervals.

During periods of very severe epidemics, where there is very intimate exposure of healthy people to the sick, and where multiple infections of meningitis are occurring, immediate protection may be obtained by means of a small dose of 5 c.c. of the antimeningitis serum injected subcutaneously. The protection afforded by this measure only lasts for a period of about two weeks.

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CHAPTER II

ERYSIPELAS

GEORGE DOCK

Definition.—"Erysipelas is an infectious disease characterized by a peculiar inflammation of the skin, with fever and other general symptoms," caused by a streptococcus discovered by Fehleisen.

Etiology.—Erysipelas, as observed clinically, is always caused by streptococci culturally and morphologically identical with Streptococcus pyogenes. In some lower animals other germs, especially pneumococci, staphylococci, and colon bacilli, cause similar lesions, but cases in human pathology are very rare. Von Leube has described a pneumococcus case caused in a patient with pneumonia by boring the nose.

Predisposing and Assisting Causes.—Erysipelas was formerly an almost inevitable complication of operations and wounds in surgical wards. Since the advent of surgical cleanliness it has become practically extinct as a surgical disease, and is seen usually in private practice, in medical wards, and in asylums. It is kept out of large wounds without special precautions other than aseptic technic, but it occurs without discoverable cause, or following a trifling scratch or abrasion. An aged physician, rising suddenly, injured his scalp on the sharp point of an electric light bulb. Severe erysipelas followed immediately. It may take its starting point in an eczema, acne, or lupus; in the excoriation on the lip from a rhinitis; in a pruritus of the perineum or vulva; in a vaccination wound; after leech bites; boring for earrings; the umbilical cord; the uterus post partum. Septic diseases of the nose, throat, and ears are among the most important causes in medical wards, and the danger must always be borne in mind. In so-called cryptogenetic cases it is not necessary to assume an unseen wound. The germs are often present on the body. A local alteration of nutrition in the skin or mucous membrane, or the assistance of another germ, such as the colon bacillus, may furnish a favorable seat, or more favorable conditions for the multiplication and increased virulence of the germs.

Erysipelas is still spoken of sometimes as a contagious disease, in the sense that it is communicated through the air, or without direct contact.

As the facts on which the belief is based occur more often in private houses than in hospitals, and more often in medical than in surgical wards, it is more likely that casual transfer has taken place. The streptococci are easily destroyed where they are known to be present, but can live long under conditions that include careless handling of dressings, eating and drinking utensils, and other small articles of personal use. It has been thought to have been transmitted by body lice in the plush seat of a railroad car.

Individual predisposition to erysipelas is an important but obscure fact. The disease occurs chiefly in early middle life, but is not uncommon at the extremes of age. It is more frequent in women than in men. The cold, wet months of late winter and early spring furnish a large proportion of cases.

Pathologic Anatomy and Pathology.—Erysipelas produces a serofibrinous inflammation of the skin, the cocci growing in large numbers in the lymph spaces. Their soluble toxins cause degenerative changes of various kinds and degrees. The process varies in depth in different cases and may extend deep in the corium. The process also extends laterally and involves the blood-capillaries and lymphatics. It may reach the regional lymphatic glands, but rarely causes general septicemia or metastatic foci. Suppuration and necrosis are possible results, but suppuration, when it occurs, is sometimes the result of secondary infection by Staphylococcus aureus or albus. Leukocytosis is almost always present. The general symptoms are due to the toxins produced by the germs. Coleman, Barr and Dubois found an increase of metabolism of from 19 to 42 per cent above normal during the fever. The increase of metabolism is roughly proportional to the degree of fever. They also observed that the change in rectal temperature is not always an accurate index of the change in average body temperature in erysipelas.

Symptoms.—The earliest symptoms of erysipelas are the common phenomena of sepsis—malaise, loss of appetite, lassitude, or febrile exhilaration, etc. The stage of incubation varies from two days to two weeks (fifteen to sixty hours according to Gay and Rhodes). A distinct chill is almost constant as the first marked symptom. Sometimes there is a series of slight chilly feelings. Vomiting, nausea, prostration, and fever then follow, the temperature reaching from 102° to 104° F., or even more, and continuing as a remittent or intermittent fever. Delirium is often present during the early febrile stages. For one or two days the diagnosis may be in doubt, especially if exposure is not known. Lymphatic tenderness may be present, or there may be pain or a feeling of tension in the skin without evidence of trauma or infection. Epistaxis occurs sometimes when the primary focus is in the nose.

The characteristic lesion is a flat swelling of the skin, with a distinct abrupt edge, a rather rough but glistening surface, of more or less distinct red color. It occurs chiefly on the face, in the region of the nose, ear, mouth, and, in typical "medical" erysipelas, produces a butterfly-shaped area of disease, with its center on the nose. The affected skin feels hard and stiff. It enlarges by irregular advances at the edge, and is often checked where the skin is closely adherent to the deeper tissue. The swelling is greater where the deep tissue is loose, as in the eyelids. The scalp is often involved, and when so, temporary loss of hair follows desquamation. The surface may become vesicular, or may suppurate or become gangrenous, the deep tissues may be involved, causing an inflammatory edema, or may go on to abscess formation.

The fever lasts during the active stage of the skin process, the whole length of the disease being from a few days to two weeks, or longer in some "migrating" cases. After the inflammation subsides, desquamation follows. The affected area may long remain hyperemic.

Erysipelas of the nose, mouth, and pharynx is occasionally observed. It does not require special description, as the phenomena and treatment are those of septic inflammation, and the diagnosis of erysipelas should not be made unless there is an extension to the skin.

Complications and Sequels.—Suppuration of adjacent sinuses is not uncommon; albuminuria with casts is almost constant, but does not often result in permanent kidney disease. Affections of the heart and pericardium are rare; pleurisy and pneumonia also. Peritonitis has been observed, especially in cases affecting the female genitals. Serous effusions in one or many joints may occur, less frequently suppurative arthritis.

Diagnosis.—The diagnosis of erysipelas is not difficult after the skin lesion appears. Before that, all infections must be thought of and searched for by appropriate methods of examination.

Prognosis.—The prognosis is extremely variable. In previously healthy individuals, not in the extremes of age, erysipelas is, even if severe, usually followed by complete recovery. In the young—all newborn and almost all under one year die—in the old and the cachectic, in diabetics, hard drinkers and arteriosclerotics, it is dangerous—often fatal. Erysipelas of the mucous membrane is serious; erysipelas of the scalp not always so.

Erysipelas has been supposed not to produce immunity, and often seems to increase the disposition to renewed infection. Many cases are known of yearly relapses, or even much more frequent ones. Gay and Rhodes have shown in experiments on rabbits a local tissue immunity, giving protection against intradermal reinoculation after three weeks for at least three months. Vaccines killed by heat or alcohol do not protect against the local lesion, but oil vaccine frequently protects. Several injections of the original living stock culture, which produces no lesion, protect against the passage strain.

TREATMENT

There is no internal treatment for erysipelas. The iron and quinin so long used and still recommended are useless against the disease. In patients with other diseases appropriate treatment may be continued, unless contra-indicated by special symptoms.

General measures should be carried out as for other diseases. The vomiting of the onset should be allayed by draughts of hot water. A mild cathartic is usually beneficial.

The diet should be simple and limited to liquids for the first few days at least. Water or dilute fruit juices should be given freely. It is usually more comfortable for the patient to be in a cool, rather dark room.

Symptoms may be met as under other conditions. The fever, as a rule, does not require treatment, but, if it seems to, small doses of such antipyretics as phenacetin (gr. 3, gm. 0.2) may be used. Tepid sponging is beneficial, but cold, full baths are not necessary, except in highly septic cases.

For headache, restlessness, or sleeplessness, a full dose of sodium bromid (gr. 40 to 80, gm. 3 to 6) should be given as necessary. If sleep has been lost, a full dose of chloral hydrate may be added (gr. 15, gm. 1.0).

In potators the heart must be watched. Caffein, digitalis, or camphor hypodermically should be begun as soon as the need is suspected.

Serums and vaccines have been used, including the serum of patients recovered from erysipelas, in doses of 8 c.c., but without showing real efficacy. Fornaca thinks the serum is not bactericidal, but lessens the virulence of germs. Both homologous and heterologous sera and vaccines, simple and polyvalent, have been used. Diphtheria serum has also been used by Chapiro, Tomaselli, and others, with good results. It must be remembered that erysipelas is a disease of varying severity and irregular course. Many cases begin severely, but soon subside. All kinds of drugs as well as charms and incantations have been used with great satisfaction to their originators, but one should meet claims for sera and vaccines with the same criticism that we do iron, quinin, and other drugs, and require definite results comparable to that of quinin in malaria, or diphtheria antitoxin in diphtheria, before accepting recommendations or following them in practice.

Local treatment offers many methods. All sorts of local sedatives have been tried, dry, wet, and in unguents. Some old popular remedies, like brewers' yeast, are revived from time to time under the stimulus of hypothesis. Among all local preparations, ichthyol, in the opinion of the writer, deserves first place. It is astringent, and so lessens the painful sense of swelling in the skin; it has an antiseptic action in the test tube, and, although in the body this can hardly be very great, the results in practice are apparently superior to those of simple compression methods, or to antiseptics like iodin. It can be used as an unguent, diluted with vaselin—1 to 4—or as a varnish (Unna's formula):

℞

Ichthyol	40.0
Starch powder	40.0
Egg-albumin	1.5
Water to make	100.0

or combined with collodion or traumaticin, 1:3 or 1:4.[1]

Before using ichthyol in any form the skin should be carefully washed with soap and water. The ichthyol should then be rubbed or painted on, beginning about an inch beyond the margin of inflammation and covering all the affected part. If the margin advances, the ichthyol should be applied beyond it as often as necessary. If relapse occurs the same treatment should be repeated.

The writer would like to recommend another method of treatment, based upon a different principle. I refer to the artificial hyperemia of Bier. This can be brought about by hot air from any convenient source, but is most conveniently done by the bandage kept on continuously, either eleven hours or twenty-three hours at a time, with an intermission of an hour. In the case of erysipelas of the face a gauze bandage should be put on the neck and a garter elastic, furnished with hooks and eyes, fastened on with just enough constriction to cause moderate congestion of the face without mottling and without pain. On the extremities the usual compression bandage should be used.

More heroic methods of treatment have been almost entirely abandoned in practice, though not in textbooks, and in severe cases may at times be resorted to. The chief methods are those of Hueter and Kraske-Riedel, and consist in the use of free incisions into the affected part, with compresses saturated with carbolic acid, 3 per cent, or bichlorid of mercury, one per one thousand.

Treatment of Complications.—Mild vesiculation requires no treatment. If suppuration occurs the parts should be kept as clean as possible. Ichthyol or other antiseptics may be used. Gangrene is to be treated on surgical principles.

Meningitis is to be suspected when cerebral symptoms are severe. It is rarely present, but when it is it should be treated as under other circumstances.

The healing of other diseases by erysipelas toxins does not seem to belong to this chapter, but it may be mentioned that various diseases besides tumors have seemed to be favorably influenced by an attack of erysipelas. Feilchenfeld has reported the healing of blennorrhea of the lacrimal sac, Stadler one of pernicious anemia.

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[1] A mixture of equal parts of ichthyol, lanolin and water makes a pasty mass easily applied.—Editor.

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INFECTIONS DUE TO FILTER-PASSING VIRUSES

CHAPTER III

ACUTE POLIOMYELITIS

George Draper

The treatment of acute poliomyelitis falls naturally into two distinct phases. This division depends upon the fact that the disease itself definitely expresses two entirely distinct sets of phenomena. The first of these has to do with all the processes of an acute infectious disease; the second with the phenomena of injury to certain specially selected portions of the central nervous system. A comprehensive discussion, therefore, of the treatment of this extraordinary malady involves necessarily a consideration of both phases. In a general way the tendency to specialization in medicine has more or less determined the branches of the healing art which are concerned with each one of these phases. The first originally became the responsibility of the family doctor who was called to see what the old English physicians termed "the paralysis of the morning." Within the last decade, as the result of the laboratory investigations of Flexner and Amoss, Landsteiner, Levaditi, and others, the management of the acute phase of infantile paralysis has fallen more and more into the hands of students of infection and immunity. The management of the secondary phase of the disease, that which is concerned with injury to the central nervous system, the responsibility for which was assumed by the neurologist, is now dealt with almost exclusively by the orthopedic surgeon.

Prevention.—During epidemic periods, where the virus is supposedly universally distributed within the community, it is a grave question whether segregation or even hospitalization will have much limiting effect upon the spread of the disease. Obviously, every epidemic must start with an initial case, so that if that initial case could be caught and secured, and all its contacts secured, the possibility of a check of the spread is conceivable. But the difficulty with this particular malady is that there are a great many more carriers of the disease that go about unrecognized than there are apparent cases. Furthermore, the very nature of the disease, with its crippling action, automatically tends to limit the excursions of the infected individual, while his apparently healthy brothers and sisters, harboring an active virus in the nasal and buccal secretions, wander about uncontrolled. Exceedingly drastic regulations, such as placing a rigid quarantine on every member of the household with the exception of one breadwinner, apparently has had a checking influence upon the epidemic in several smaller localities where this method has been tried. But such a procedure is very difficult to carry out. In small communities it may be worth while to try this rigid quarantine for a couple of weeks. In the larger communities it is almost hopeless to attempt a control in the spread. Certainly the wild procedures which were instituted during the epidemic of 1916, such as limiting the travel of individuals below a certain age and policing the roads in order to hold up automobiles passing between counties, are not only futile but exceedingly irritating to the public. They undoubtedly create a state of panic which is not justified by the menace of the disease itself. That the virus is contained in the nasal and buccal secretions and in the dejecta has been established. Consequently if the transfer of the nasal and mouth secretions and the bowel content from one individual to another could be stopped, some effect on the spread of the disease might be achieved. But the prevention of the spread of these substances from one individual to another is one of the most difficult things imaginable.

It is only necessary to recall how widespread is the neglect to wash the hands after using toilet paper, and how often the welcoming hand, still moist from blowing the nose through a handkerchief, is extended in friendly greeting (not to mention kissing, coughing and spitting) in order to realize the futility of the usual quarantine measures in this or any other disease whose virus is human borne. The slow process of education really is the only solution of the problem of preventing epidemics of acute poliomyelitis, just as it has been of tuberculosis.

Treatment of Acute Stage of Infantile Paralysis.—In order to understand the principles of treatment which have been established for the acute phase of the disease, it is necessary to review briefly the mechanism of the infection. According to the work of Flexner and Amoss the route of the virus has been more or less clearly shown to be via the choroid plexus and the posterior root ganglia. Whether or not the disease is primarily and solely hematogenous with a secondary penetration of the meninges, or whether the route is a direct infection of the nasal mucosa and so on through the sheaths of the olfactory nerve into the meninges, is still a mooted question. There is a great deal of presumptive evidence that the former is the more frequent mechanism. One of the chief arguments for this view is the proved non-paralytic type or so-called abortive type of the disease. While there is no definite proof of the exact portal of entry of the virus, the fact that it is primarily distributed through the blood-stream and secondarily penetrates the meninges receives strong support from the history of the acute stage of the paralytic form of the disease, the early hours of which are analogous to the whole extent of the malady in the abortive cases. During these early hours the picture is much like that of any other acute infection, so far as the general symptoms of temperature, malaise and prostration are concerned. In addition to these general symptoms of fever there are, however, certain somewhat more specific characteristics which have attracted the attention of those who have seen large numbers of cases. These are peculiar nervous irritability, and a resentfulness which is expressed when even the kindliest hand is put forth to help. Somnolence, alternating with increased nervous stimulation, is likewise characteristic.

Upon this preliminary set of phenomena there very rapidly supervenes the picture of an early irritation of the meninges. This first shows itself in the pain and tenderness related to the posterior spinal route ganglia and is best elicited by anterior flexion of the spine. It is not a reflex rigidity which meets the effort of the examiner to flex the spine anteriorly, but a voluntary resistance on the part of the child to this anterior flexion of the spine, because it hurts. Indeed this protective act of the child to prevent anterior flexion is frequently carried to the opposite extreme, so that a true opisthotonos appears. Following upon this primary involvement of the ganglia, which has been shown in the laboratory animal to be one of the earliest locations to receive the penetrating virus, there is a more or less rapid involvement of the central nervous system. As the inflammatory process advances, the production of spinal fluid increases in amount and there is an outpouring of cells with the obvious result of increased pressure within the cerebrospinal space. The next development is the involvement of the anterior horn cells by the advancing infection, with the production of a train of symptoms leading from muscular twitchings through various degrees of muscular weakness to complete paralysis. Parallel with these events one finds every variety of change in the deep tendon reflexes. The location of the paralyses naturally introduces some complicating elements in the management of the case, especially if the paralyzed muscles are related to important physiologic processes, such as swallowing or breathing. The specific details for the management of these situations will be referred to later.

So, then, there are presented for treatment, first of all, the picture of an acute febrile state; secondly, a stage of pain and general irritability; thirdly, the involvement of the meninges with the attendant production of spinal fluid, resulting in increased pressure within the cerebrospinal space.

If each of these stages were to be treated non-specifically, then, obviously all that could be done in the first stage would be to apply the simple symptomatic methods which have been used in all febrile conditions; so that the question of specific therapy must be brought up for discussion at this point.

It is well known, as a result of the studies of Flexner and Amoss, Landsteiner, Levaditi, and others, that the virus of poliomyelitis can be rendered inert or neutralized by the action of serum taken from recovered cases. It is perfectly easy, as these authors have shown, to protect monkeys from many times the lethal dose by the use of such serum. It was natural, therefore, that Netter, in 1912, should have attempted the treatment of an acute case of the disease by the injection of human serum taken from a recovered case. Though the number of cases reported by Netter was small, he felt very distinctly encouraged by the results. During the great epidemic of 1916, Amoss, in Westchester County, and the writer, on Long Island, New York, used the serum of recovered cases in a large number of instances. The conclusion reached in both groups was that, while the serum was not established as an absolutely definite cure, the results seemed to justify the feeling that if it were used early, within the first twelve hours after the acute onset, it undoubtedly exerted a protective influence. Amoss felt that the use of serum intravenously as well as intraspinally was of added benefit, largely because of the increased concentration of the antibodies on the blood side of the injured choroid. Tables showing the therapeutic results in these two groups appear in the writer's book on the subject.

The technic of the intraspinal injection in this condition is similar to that used for any intraspinal work. The serum is obtained by bleeding the recovered case and separating the serum in the usual way in the laboratory. As much spinal fluid as can be drawn off is removed from the patient and then not more than 10 or at most 15 c.c. of serum is permitted to flow back into the spinal canal. The intravenous injection of the same serum should be carried out just subsequent to the intraspinal injection. Within the last two or three years the writer has treated a number of cases in the very early stage and used large quantities of serum intravenously. In several instances two doses of 100 c.c. each, separated by an interval of from ten to twelve hours, have been given. Each of these cases received but one intraspinal injection.

There is no doubt in the writer's mind that such use of recovered serum, in large quantities and at a very early period in the disease, offers a real hope for the prevention of paralysis.

There is almost always a severe aggravation of symptoms following the intraspinal injection of recovered serum in these cases. Headache, rise of temperature and general malaise become relatively much more marked than one ordinarily sees in cases of cerebrospinal meningitis following intraspinal injection of antimeningococcus serum. This reaction has always seemed a rather inexplicable one in view of the fact that it is more intense in the case of the homologous serum.

It is important to remember that the type of the disease is constantly changing and that the picture which we see to-day is rather different from that which was met with during the great epidemic in 1916. Consequently the matter of early diagnosis remains always an exceedingly difficult problem. But it is a good rule to see to it that any patient is punctured who presents an unexplained febrile disturbance, and shows the peculiar irritability and slight tenderness on flexion of the spine. Within the last two or three years an apparently increasing proportion of young adults have been developing the disease and it is exceedingly important not to let the malady masquerade, as it often does, under the diagnosis of bronchitis or typhoid fever.

Any discussion of the serum therapy of acute poliomyelitis would not be complete without mention, at least, of the antistreptococcus serum prepared by E. C. Rosenow of Rochester. It is difficult to place great belief in this serum because it fails to neutralize the known virus of poliomyelitis, which is neutralized by the serum of recovered human beings or monkeys. In other words, the laboratory has failed to prove a specific neutralizing substance in the Rosenow serum. Consequently the laboratory results and the clinical results with this serum reported by Rosenow are paradoxical. A complete discussion of the whole subject of the Rosenow serum can be found in the very extensive literature which deals with this particular question. The writer's feeling about the Rosenow serum is that it is an unsafe therapeutic agent in this disease. The reason for this belief rests upon the fact that the sensitizing and shocking potentialities of foreign serum always constitute a menace. In meningitis, where the lesion involves the membranes surrounding the brain and cord, this menace may not be so great as in the situation found in poliomyelitis, where the lesion involves much more intimately the delicate anterior horn cells. Here any slight and sudden increase in congestion of the tissues might precipitate a fatal collapse of the cells.

If the result of serum therapy is successful, the disease picture rapidly subsides into one of a convalescence from any ordinary febrile state, but it is important to maintain a rest period for a far greater length of time than is ordinarily necessary with simple infections, for the reason that irritation of the central nervous system may have advanced to a considerable degree.

But if the specific therapy fails, or if no specific therapy is used, a great variety of therapeutic problems may develop. Obviously we have no means of staying the advance of paralysis. All that can be done is to keep the patient as much at rest as possible.

The matter of feeding will be largely determined by the patient's own desires. It is very remarkable, however, after the fever has gone and the acute phase of the disease has ended, to see how rapidly children regain their appetites and clamor for food. This is a characteristic feature of the recovery period. Where the paralysis involves the muscles of deglutition it is necessary to institute feeding by gavage. This is best done in small children by the nasal tube and in larger ones may be done directly by a stomach tube. On the whole, the nasal tube is rather to be preferred as it seems to produce less the sense of gagging. At best these cases of deglutition paralysis are very discouraging and require great patience on the part of doctors and nurses, but I have never seen a case of deglutition paralysis which did not recover.

When the muscles of respiration are involved it is necessary to provide the child with as much encouragement and moral support as possible. To any one who has observed the frightful struggle which children carry on with the advancing paralysis of respiration, the realization comes of the futility of any effort to help. No one knows as well as the child what is needed to meet the situation, and all the tact of which the nurse is capable is required to let the child feel that every assistance is promptly at hand when it wants it, but that nothing unnecessary will be done which may in any way interfere with the difficult process of getting a breath. In those cases in which the diaphragm alone or the intercostal muscles alone are involved, recovery is often possible. Indeed I have seen a child go through an acute lobar pneumonia with a paralyzed diaphragm.

Disturbances of the bladder muscles must be met, as the occasion arises, by catheterization.

Management of Paralysis.—While there are many different schools in the matter of the management of the later stages of paralysis, I think it is universally agreed that the only wise course to pursue during the first few weeks of the paralysis is that of complete rest. The paralyzed limb should be placed in the positions which put the least tension upon all muscles, and the muscles whose antagonists are paralyzed should be prevented from contracting by appropriate splints and posture. During the very early days of paralysis there is often a great deal of pain associated with the paralyzed muscles. This is best treated by keeping the limb wrapped in cotton wool and very warm. As a rule, some one posture provides greater comfort than any other. This may be found by chance or by careful experimentation by the nurse. As time passes and the question of how much power is to be expected from the muscles is brought up, the matter of more active measures of treatment naturally arises for discussion. Here it is that there are certain differences in opinion in the matter of treatment. Some of the orthopedic surgeons feel that it is wiser to maintain the rest policy very much longer than others. Probably there is no successful universal rule, but it is safer to err on the side of prolonging rest rather than start passive motion and massage too early.

While there are no proved permanent residual effects in the psychic realm, one often sees more or less nervous irritability and apprehensiveness on the part of the child. This state may last for a variable length of time and should be recognized as a definite part of the recovery process. Except for surrounding the child with an atmosphere of serenity and encouragement, there is nothing specific to be done for the condition, but the child should be maintained in a resting phase, so far as sending it back to school and other mental activities are concerned, for a far longer period than would ordinarily be prescribed in the case of infectious diseases which had not directly menaced the central nervous system.

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CHAPTER IV

EPIDEMIC ENCEPHALITIS

HUBERT S. HOWE

Epidemic encephalitis is a disease which produces a non-suppurative inflammation in the nervous system. It was first observed by von Economo of Vienna, in 1917. In the spring of 1918 cases were observed in France, Germany and England. In the fall of 1918 it appeared in America, and has since invaded all portions of the world.

Etiology.—Epidemic encephalitis occurs sporadically throughout the entire year, but seems to have a decided seasonal incidence, becoming most prevalent in the winter. The incidence curve starts to rise in December, continuing through January and reaching the peak in February, after which there is a rapid fall in March.

The sexes are equally affected. No age is exempt. Of 1,273 cases reported by the British Ministry of Health, there were approximately 15 per cent in the first decade, 25 per cent in the second, and 15 per cent in each of the third, fourth and fifth decades, the remaining 15 per cent occurring after the age of fifty. Social condition and occupation seem to have no influence upon the incidence of this disease.

Symptoms.—Many attempts have been made to classify the disease into types on anatomic, clinical and durational bases, but without much success, as the manifestations are protean and variable, and the course irregular.

The incubation period has not been determined but, judging from the instances where direct contagion has seemed to be present, it is between ten and twenty days. Sudden onset of severe symptoms is observed in some instances. Generalized or jacksonian convulsions, apoplectic attacks, sudden strong emotional or psychical disturbances, or even unconsciousness may be the first evidence of illness. Usually, however, the onset is gradual. The first symptoms may be those of a general infection which may readily be mistaken for "a cold" or "the grip." Headache, anorexia, vomiting, fever, constipation and loss of appetite are frequent. In a few days localized pains appear, usually radicular in localization and severe in character. If the infection is severe, delirium may occur which may be active or have one of the peculiarities of the lethargy, namely, the patient may answer questions and act in a normal manner when engaged in conversation, but will return to his hypomanic activity and delirium unless diverted.

In a week or ten days the lethargy, from which the disease has received its popular name, supervenes. At first it is simply a drowsiness with a tendency on the part of the patient to sleep unless his attention is maintained by something in his environment. Later it deepens into either a continuous sleep from which he is easily aroused, a stupor or coma. At this time there are usually other signs of involvement of the nervous system. Some degree of fever is present in the greater proportion of patients. It is usually continuous, varying from 100° to 103°, and its average duration is about two to three weeks. High fever is of serious import. A constantly rising temperature with corresponding acceleration of the pulse and respiration is ominous, as is hyperpyrexia, which is nearly always fatal. During the febrile period, a moderate leukocytosis may be present, there being an increase in the total number of white cells with a relative increase in the polynuclear leukocytes.

Cranial nerve palsies are often the first sign of localized involvement of the nervous system. Optic neuritis or some evidence of it is present in about 20 per cent of cases. This may be a slight reddening of the disc with blurring of its margin and an arterial narrowing. Palsy of the third nerve is very frequent and may be a partial external or internal ophthalmoplegia, or a combination of the two. Ptosis and weakness of accommodation is the most frequent combination and when present is of much importance in diagnosis. Weakness of the sixth nerve occurs, but not so commonly as involvement of the seventh. The facial paralysis may be bilateral and is usually slight, but it should not be confused with the facies of stupor or the rigidity which is a part of the Parkinsonian syndrome.

The portion of the nervous system involved by the virus of epidemic encephalitis with great frequency is the corpus striatum. Lesions here produce the disturbances of tone, suppression of the automatic and associated movements, various types of tremors and automatic movements. The agitans tremor of Parkinson's syndrome, and major and minor choreoathetoid movements are probably produced by a lesion in the corpus striatum. Other types of involuntary movements are sometimes seen—myorhythmic and myoclonic—in which the seat of the lesion is uncertain. In the myorhythmic movements there is a more or less regular contraction of a group of muscles producing a definite movement such as partially closing the hand, contraction of the facial muscles, champing or lateral movement of the jaw. The myoclonic movements are rapid lightninglike contractions of a single muscle or a portion of a muscle, rather than of a synergetic group. These contractions may involve any muscle, but those of the trunk, particularly of the abdominal muscles and diaphragm, are possibly more frequent than those of the extremities. There is some evidence that the myoclonic movements are the result of irritation of the anterior horn cells of the spinal cord or other portions of the lower motor neuron.

Evidence of involvement of the pyramidal tract is often seen. Slight or moderate weakness of an extremity, with increased deep reflexes and a positive Babinski sign, is more usual than a definite hemiplegia.

Clinical Pathology.—The cerebrospinal fluid is clear and colorless. At the onset and during the periods of exacerbation there may be: (1) an increased cell count, the cells being lymphocytes and large mononuclears; (2) a slight increase in protein content, but at times less marked than would be expected with the increased cell count.

Often the spinal fluid is normal throughout the entire course of the disease.

In the subacute and chronic stages, there may be a slight increase in the chlorid content (0.8 per cent) and possibly a slight lymphocytosis and increase in protein.

The sugar content is normal or increased. Hyperglycorrhachia has been said to be characteristic of this disease, but further observations show that similar sugar percentages are found in many other diseases of the central nervous system. This feature is only of value, therefore, in the differential diagnosis of encephalitis and tuberculous meningitis where the sugar content is decreased.

The blood count does not show constant alteration. In the acute stage there is a moderate leukocytosis, the average count being 12,000 to 15,000 with a slight increase in the polymorphonuclear leukocyte percentage.

Duration.—The course of this disease is in no way uniform. The approximate duration of the acute stage is all that may be roughly estimated. The fever period may be very short, that is, only a few days; or it may be prolonged for eight or ten weeks; but two weeks is the average time. The lethargy may be short, prolonged, or relapsing, but usually in the acute stage lasts about three weeks. No time limits can be set for the palsies or involuntary movements.

The acute period of the disease is generally about three or four weeks, and either death intervenes or improvement commences within this time. In approximately 50 per cent of the fatal cases, the termination is during the first two weeks, and in 80 per cent during the first month. There are no available data at present to prognosticate the duration of the sequelæ. It is also impossible to determine when a patient is free from the danger of a relapse, as serious sequelæ have developed more than two years after apparent complete recovery. Of the sequelæ, the paralysis agitans syndrome is the most frequent as well as the most protracted form.

Prophylaxis.—The limited state of our knowledge concerning the virus and the manner of propagation makes it impossible to give any method of prevention. The little evidence of contagion indicates that the disease is of a low grade of infectivity. That infection by contagion has occurred in some instances seems fairly well established. It is therefore desirable that the patient should be isolated from all who are not necessary for the proper nursing during the acute stages of the disease. As the virus may be present in the nasal secretions and saliva, these discharges should be disinfected and the gauze used in connection with the toilet of the nose and mouth should be destroyed. One instance is reported where infection may have taken place through clothing, so it would seem well to have the patient's clothes disinfected. It has also been recommended that persons coming in contact with the patient should use an antiseptic spray or gargle.

Experimental Pathology.—As soon as epidemic encephalitis became prevalent, attempts were made by many workers to produce the disease in animals. These were mainly unsuccessful. In 1919, Strauss, Hirshfeld and Loewe produced a meningo-encephalitis in rabbits by intracerebral inoculation of material derived from the nasopharyngeal washings of patients with epidemic encephalitis. A remarkable feature of their findings was that they succeeded so easily and in such a high percentage of cases that they even proposed their method as a diagnostic test. Their observations were in part confirmed by Levaditi and Harvier and a few others. The complete failure of other careful investigators made the whole question an enigma until the recent research work on the virus of herpes appeared. Much experimentation has been carried out by Levaditi, Harvier and others with the herpetic virus, and it seems to be similar to or identical with the so-called encephalitis virus. Therefore it would appear that either epidemic encephalitis is due to a form of herpetic virus, which seems improbable, or that the positive results of experimental animal inoculations have been due to the herpetic virus and have nothing to do with epidemic encephalitis. This latter seems the more probable explanation, but it is a matter that subsequent experimentation will have to elucidate.

Morbid Anatomy.—The gross appearance of the brain usually presents nothing abnormal, but the cortex, and on section the surface, may be reddened from capillary congestion. The large vessels stand out prominently. Small punctate hemorrhagic areas are seen in the midbrain and pons. Microscopical examination shows an infiltration of the adventitial lymph spaces with small round cells. This is not found in all portions of the brain and frequently many sections have to be examined before any alterations other than congestion are seen. The brain stem and basal ganglia are the parts most vulnerable. There are areas in the gray or white matter where collections of small round cells are seen. The motor cells in the involved areas show acute cloudy swelling, and at times severe grades of degenerative changes. Some of the nerve cells in the severer stage of dissolution are surrounded by neuronophages.

Diagnosis.—The cases that conform to the classic type with ocular palsies, fever and lethargy, are characteristic enough to make the diagnosis comparatively easy. Abortive or atypical cases without lethargy, especially when occurring during interepidemic periods, render the diagnosis more difficult.

The conditions which offer the greatest difficulty in differentiation are *tuberculous meningitis, brain tumor and brain abscess.*

Tuberculous Meningitis.—Careful examination of the spinal fluid will usually be sufficient to make the differentiation between tuberculous meningitis and encephalitis. In the former the spinal fluid is always altered; while in encephalitis it is often normal. The pressure at the onset of tuberculous meningitis is markedly increased. The cells are mainly lymphocytes, but polymorphonuclear leukocytes are almost constantly present, while they are almost uniformly absent in encephalitis. The protein content is much increased in tuberculous meningitis and but slightly so in encephalitis. In tuberculous meningitis the sugar content is decreased or absent, while it is normal or increased in encephalitis. The chlorids are lessened in tuberculous meningitis, being below the normal 0.73 per cent; they are normal or increased in encephalitis. On standing, the spinal fluid in tuberculous meningitis shows the formation of a spider-weblike pellicle which, if carefully examined, may reveal the tubercle bacillus. Similar coagula are rare in the spinal fluid of epidemic encephalitis.

Brain Tumor or Abscess.—The presence of continued severe headache, repeated vomiting and frank choked disc are evidence in favor of brain tumor. In encephalitis the lesions tend to be bilateral or diffuse, while in tumor or abscess they are more apt to be unilateral and localized.

Prognosis—*Prognosis as to Life.*—The general mortality percentage has varied greatly in different epidemics. In a report of the British Ministry of Health on 1,273 cases, the mortality was 48.3 per cent. Wechsler computed statistics of 850 cases and found a mortality of 21 per cent. In infancy the death-rate is high. The mortality is lowest in the second decade, but rises steadily as the age increases, reaching 80 per cent in the seventh decade.

The patients with symptoms of a severe general infection show a high mortality. Profound stupor, interrupted by emotional outbursts, is ominous. Deep coma may continue for days but even if unaccompanied by fever is of serious import. The greatest mortality occurs within the first three weeks of illness. Most of the patients who survive four weeks will live, but they may have a long and tedious convalescence.

Prognosis as to Complete Recovery.—It is at present impossible to get accurate statistics as to the percentage of patients who are completely and permanently restored to health. It appears that at least 50 per cent suffer some disability, such as loss of ambition, drowsiness or insomnia, defective memory, character alterations, partial or complete paralysis agitans syndrome, or some other serious lesions of the nervous system. Any prognosis as to the ultimate outcome should be given with caution in even very mild acute attacks, as many times what seems to be complete recovery is followed by crippling disorders after a period of one or two years.

TREATMENT

General Measures.—In the treatment of encephalitis, drugs play a minor rôle. In the acute stage the general management of the patient is of extreme importance. If possible he should be removed to a hospital. The room should be large, well ventilated, and in as quiet a part of the hospital as possible because, even though the patient is in a state of lethargy, he may be easily aroused, annoyed and made restless by noise. The amount of light admitted should depend upon the patient's comfort. In the early stages photophobia is frequent and necessitates darkening the room.

Nurses should be in constant attendance. In this connection it is important to remember that patients in stupor may suddenly have outbursts of excitement and attempt to get out of bed. This occurs most frequently at night.

The amount of urine passed and the periods between voiding must be carefully noted, otherwise retention with overfilling of the bladder may develop. Facilities for catheterism should always be at hand.

The patient should be kept absolutely quiet in bed. This should be insisted upon as soon as the disease is suspected, even if there is no fever and the patient does not feel ill. No patient with an acute infection involving his nervous system should be out of bed. Absolute rest is the most important element in the treatment and from the beginning the patient should not do anything for himself which involves exertion. In order to secure as complete rest as possible, visitors should be prohibited and the patient should not be aroused unnecessarily. The use of the bed-pan and urinal should, if possible, be commenced before the patient grows very drowsy, so that he may become accustomed to them. If there is difficulty in voiding in the dorsal posture, he may be turned on his side or raised to the sitting position. This is easily accomplished if he is on a Gatch bed, and, if it is insisted upon that he learn to void in this position, the difficulty will usually be overcome.

Cleanliness of the body is essential, and the back should be kept dry by sponging with alcohol and the liberal use of talcum powder. Too frequent bathing should be avoided as it is disturbing and causes some exertion on the part of the patient.

The hygiene of the mouth requires careful attention. After each feeding the teeth and tongue should be cleaned by the use of a mouthwash. A warm saturated solution of boric acid is as useful for this as any formula. Following it, the tongue and cheeks should receive an application of albolene. The preparations of glycerin and lemon, frequently advised, should not be used, as the ultimate effect of glycerin is further desiccation. If the throat is dry, albolene may be used as a gargle, or a small amount swallowed. At night, white petrolatum may be used instead of albolene.

Diet.—During the acute stage, while the patient is lethargic, the food should be fluid or semisolid. Curiously, the appetite, instead of being diminished, may be much increased so that more food is desired than before the illness commenced. Patients who have been capricious in regard to food may eat ravenously. If solid food is allowed, care must be exercised to see that it is well masticated or finely divided before administration. If it is not thoroughly masticated, indigestion and distressing flatulence result. If the patient is in a stupor he will have to be fed. In this event a diet similar to the following should be used:

8 A. M.	Milk and coffee, each 120 c.c. (4 oz.), 240 c.c. (8 oz.).
10 A. M.	Milk, hot or cold, 240 c.c. (8 oz.).
12 Noon	Oatmeal gruel, 120 c.c. (4 oz.) with milk, 60 c.c. (2 oz.).
2 P. M.	Milk, 240 c.c. (8 oz.).
4 P. M.	Oatmeal gruel, 120 c.c. (4 oz.) with milk, 60 c.c. (2 oz.).
6 P. M.	Custard with lactose (full cup).
8 P. M.	Hot milk, 240 c.c. (8 oz.).
10 P. M.	Whey, 180 c.c. (6 oz.) with one whole egg and sherry.
12 P. M.	Oatmeal gruel, 120 c.c. (4 oz.), milk, 60 c.c. (2 oz.).
2 A. M.	Milk, 240 c.c. (8 oz.).
4 A. M.	Broth, 240 c.c. (8 oz.) with one whole egg.
6 A. M.	Milk, 240 c.c. (8 oz.).

Great care should be taken in feeding patients in deep lethargy. They must be aroused sufficiently to be able to swallow before food is given, as otherwise it may pass into the larynx and trachea.

If the patient is in coma or paralysis of the throat develops so that swallowing is impossible, he should not be fed by tube as is frequently recommended. The struggling this entails has proved fatal and food has been introduced into the trachea. In this case it is best to give neither food nor fluid by mouth, but to give hypodermoclyses and intravenous infusions of sterile normal salt solution on alternate days. Instead of saline, a 10 per cent glucose solution may be used. At least 3 liters should be given daily. Water should also be given by rectum either by the drip method or by the instillation of 4 to 6 ounces at a time.

Water.—It is not as necessary to force the patient to take large amounts of water as it is in other acute infectious diseases. It is not the circulating toxins which produce the delirium or lethargy, but the direct action of the virus on the nerve cells plus edema. Infusions of hypertonic solutions which tend to reduce this edema seem to be of value. It is necessary, however, to see that the patient gets sufficient fluid, as the sensation of thirst cannot be depended upon. A record of the fluid intake should be kept in order that one may be certain that 3 liters are taken in each twenty-four hours.

Medicinal Treatment.—There is no specific drug treatment for epidemic encephalitis. Urotropin has been recommended but, as it is inert in alkaline solutions, it is difficult to understand how it would be of value. Potassium iodid has also had its advocates, but has not proved of definite value. At present all medicinal treatment must remain empirical and symptomatic.

Serum Treatment.—Autoserum therapy has been recommended by Brill and others. Brill's technic is as follows: Six to 100 c.c. of blood is obtained from the patient. This is collected in a sterile flask and allowed to stand until the serum has separated. It may be separated by centrifugalization if it is to be used immediately. This may or may not be inactivated. Recently Brill has discarded inactivation. Twenty-five to 30 c.c. of spinal fluid is withdrawn by spinal puncture and replaced by a similar amount of serum. Serum from recovered or convalescent patients has been given intraspinally and intramuscularly, but has not been used extensively enough to demonstrate its value. Antidiphtheritic serum and antitetanic serum and horse serum have their advocates, while Collatino and Vegni recommend the subcutaneous injection of convalescents' cerebrospinal fluid.

Special Measures.—The intravenous injection of hypertonic solutions causes a decrease in intracranial pressure, and an amelioration of the symptoms in some cases, probably due to a lessening of cerebral edema. For this purpose 250 to 350 c.c. of a 25 per cent glucose solution is administered intravenously every day.

Netter's Fixation Abscess.—This measure has no advocates other than its author, though it has been used by others. For this purpose, 1 to 2 c.c. of turpentine is injected into the outer portion of the thigh. If there is no reaction within a few days, the injection is repeated. The resulting abscess is incised or aspirated on the fifth or sixth day.

Frequent spinal drainage has been of value in some instances, and is to be especially recommended when the spinal fluid pressure is increased and when the cell count is high or there are other alterations.

TREATMENT OF SPECIAL CONDITIONS

Mental Symptoms.—For the restlessness, insomnia and delirium which may occur in the early stages, the cold sponge and full wet pack are very useful measures. For the administration of the sponge, the patient, when disrobed, should be placed between blankets. Small sections only of the body are to be exposed and sponged at a time. The temperature of the water should be 90° F., for the first treatment, and reduced daily until 70° is reached. The wet pack should be commenced at a temperature of 80° F., and reduced 2 degrees daily, to 70°. In the application of the full wet pack, the sheet should be well wrung out and carefully applied so that it is in close contact with the skin and all air absolutely excluded, otherwise the aim of the pack is defeated. The duration of the pack should be one hour. The cold sponges should be given in the early morning and mid-afternoon, and the pack at night, as after it the patient will usually go to sleep. If it seems necessary to give drugs, 15 to 20 gr. of sodium bromid with 10 gr. of chloral hydrate, every four hours, is usually effective. If the delirium is violent, the most effectual remedy is paraldehyd. On account of its taste and nauseating properties, this is best administered by rectum. Four to 6 drams in 2 or 3 ounces of water to which enough starch has been added to make a thin paste should be instilled through the rectum and repeated in from four to six hours if necessary. The starch lessens the irritation and makes the instillate less fluid so that it is more easily retained. In case of violent delirium, hyoscin hydrobromid may be given hypodermatically in doses of 1/100 to 1/50 gr., and repeated in two hours if necessary. Restraint should be avoided as much as possible, as it is apt to cause strenuous resistance. It is better to allow the patient some latitude, but to protect him against injuring himself. Lumbar puncture is advisable for all patients with delirium.

For *insomnia* it may be necessary to use drugs, if the administration of hot milk, alcohol sponging or other simple measures is ineffectual. For simple sleeplessness, veronal is probably the best drug. It should not be given in large doses. It will be found that 3 to 5 gr. of veronal combined with 10 to 15 gr. of aspirin or phenacetin will be much more effective than a large dose of veronal given alone. Adalin or chloral hydrate in doses of 10 or 15 gr. is also useful.

Special Conditions in the Nervous System.—*Headache* and signs of meningeal irritation are frequently present in the early stages of the disease and are relieved by lumbar puncture. This should be repeated every two or three days if the spinal fluid pressure is increased.

Choked disk is uncommon, but when present is due to hydrocephalus and requires frequent spinal puncture.

The *headache* and *generalized aching* usually yield promptly to aspirin, phenacetin or pyramidon, or a combination of these drugs. The *radicular pains* are often very severe. They may be relieved by vigorous counterirritation, turpentine stupes or mustard poultices. Local heat in the form of hot-water bags, electric pads or baking seem of little avail. As the duration of these pains is short, it is best to give enough codein or morphin hypodermatically to bring relief.

Alimentary Tract.—Reference has been made to the care of the mouth. If the salivary glands are swollen, ice-bags should be applied.

Vomiting is frequent at the onset but rarely persistent or severe enough to require treatment. If continuous, it is probably due to hydrocephalus and may be relieved by spinal puncture.

Constipation is a marked feature of the disease and may be most refractory. Administration of saline cathartics each morning and an occasional dose of castor oil or calomel seem to be the most effective measures. Fecal impaction has occurred and its possibility should be kept in mind.

Tympanites is a frequent and distressing condition. A simple diet, with ample mastication, and measures for the relief of constipation are important preventives.

When distention is marked, turpentine stupes should be applied to the abdomen. These may be used frequently but should be alternated with stupes of simple hot water, as a constant application of turpentine may cause irritation. One or 2 ounces of turpentine may be thoroughly mixed with a quart of warm soapsuds and used as an enema. The insertion of a rectal tube will be of use if the gas is in the colon. The hypodermic administration of 1 c.c. of pituitary extract is a reliable remedy and may be used alone or in conjunction with the other measures.

Urinary Tract.—Inability to void is a common difficulty. This may be due to the position in bed, or the result of lethargy. It may be overcome by raising the patient to the sitting position or arousing him at stated intervals, urging him to void and using hot applications over the hypogastrium.

Catheterism may be necessary. Cystitis frequently follows catheterism and results in many cases from neglecting to irrigate the anterior urethra before the catheter is passed. The normal urethra, in its first three inches, swarms with bacteria which contaminate the catheter. The urethra must be washed out, therefore, and the best antiseptic wash for this purpose is a solution of oxycyanid of mercury, one part in 4,000 parts of water. Any patient who is being catheterized should be given urotropin by mouth and enough acid sodium phosphate to insure acidity of the urine.

Care of the Eyes.—If the patient has conjunctivitis, bathing the eyes with a 4 per cent solution of boric acid may be sufficient to bring relief. In more obstinate cases, instillation of a 10 per cent argyrol solution may be used. When double vision is present, one eye should be covered by a patch. Frequently a weakness or paralysis of accommodation is present, and if this is the case the patient should be forbidden to read. If he shows any tendency to use his eyes, they should be protected by dark glasses.

Convalescence.—As rest is the most important feature in the treatment of the acute stage of epidemic encephalitis, it is also of first importance during convalescence. The patient should be kept in bed until after all signs of acute illness or progressive involvement of the nervous system have disappeared. There is at times an increased cell count in the spinal fluid weeks after the patient has apparently reached a stationary stage, but unquestionably he should be kept in bed until the spinal fluid is normal. No haste should be considered in getting the patient about, as rest can do no harm and activity may produce a relapse or a progression of symptoms. When he is allowed to get up for increasing periods of time, he should be watched carefully and put back to bed at the least sign of retrogression.

The need for protracted rest has not been emphasized sufficiently in the treatment of this disease. I am sure that the ability to rest for extended periods is the main reason why private patients on the whole fare better than those treated in the clinic.

Mental rest is next in importance to physical inactivity. The psychic inertia which almost invariably follows encephalitis suggests to the patient's relatives and, unfortunately, frequently also to his medical attendant, the need of inciting his nervous system by active stimuli from without. There is little question that this inhibition of the higher psychic processes depends upon an enfeebled state of the neurons which have to do with these functions. If this deduction is correct, it becomes obvious that rest is called for until one is sure that the pathological alterations are permanent. When the patient's condition has been stationary for some weeks, he may be permitted gradually to get about and even to take moderate exercise; but his activity should never be of a kind which requires exertion or produces exhaustion. Severe physical exercise should be forbidden for at least three years after the patient has recovered or attained a stationary condition. Severe relapses have been known to follow exertion over two years after apparent complete recovery.

SEQUELÆ

The three groups of sequelæ of epidemic encephalitis which are most troublesome, are (1) the mental alterations; and (2) the abnormal involuntary movements; and (3) the paralysis agitans syndrome.

1. **Mental Alterations.**—Severe mental disturbances as sequelæ are more common in children and adolescents than in adults. Drowsiness by day and sleeplessness at night, character changes, criminalistic tendencies and behavior oddities are frequent in the young. The parents should be warned not to punish children with these disorders. Up to the present, no specific has been of avail for these conditions. It is best to isolate and protect these children from their playmates as their impishness is very apt to provoke trouble and combat. They should be allowed to sleep when they will and should be fed while awake. It is probable that most of the

children with mental changes recover, but their cure usually requires months of rest and patient care.

2. **Abnormal Involuntary Movements.**—The myoclonic movements are rarely seen at this stage. The choreo-athetoid, myorhythmic movements and paralysis agitans tremor are the principal hyperkinesias observed as sequelæ. Usually the choreo-athetoid and myorhythmic movements gradually disappear, though I have seen them continue for over three years.

3. **Paralysis Agitans.**—The sudden or gradual appearance of symptoms of paralysis agitans in a patient who has had epidemic encephalitis is an indication for complete rest. He should be kept in bed for weeks or months if necessary. Absolute rest should be maintained until it is evident that the condition is not progressing. If on getting up he is not as well as he has been while in bed, he should be put back to bed again.

The tremor and spasticity may be ameliorated by hyoscin or gelsemium. For this purpose hyoscin hydrobromid in doses of 1/400 to 1/100 gr. may be given twice or three times a day. The most effective method of administration is the hypodermatic, but it may be given orally. Some patients are exceedingly sensitive to this drug. One who has been under my care has been unable to take over 1/200 gr. at night and 1/400 gr. each morning, without developing diplopia and paralysis of accommodation. If it is not wise or feasible to administer hypodermics, the fluid extract of gelsemium may be given orally in doses of 4 to 7 minims three times daily. The patient should be constantly observed while taking either of these drugs, for cumulative symptoms (mild delirium, languor, dilated pupils with weakness of accommodation and rapid heart action) may develop, necessitating a reduction of the dose or a cessation of the drug.

When the patient's condition has become stationary, much may be accomplished by reëducation. In paralysis agitans there is an interference with the automatic movements. The patient cannot turn over in bed because he has forgotten the simple movements which are necessary to perform this act. If he is shown what movements to make, he is able to imitate them consciously and can carry out this action through the cerebral cortex rather than through the corpus striatum. With patience and the coöperation of an intelligent nurse, it is remarkable how much improvement may be obtained.

CHAPTER V

HYDROPHOBIA

Anna Wessels Williams

Introduction.—A knowledge of the treatment of hydrophobia includes a knowledge of the disease as it occurs in lower animals, as well as in man. The special prophylactic treatment, which consists in a series of daily inoculations of a specific vaccine, is comparatively long, uncomfortable, and expensive; therefore the unnecessary administration of it means more perhaps to the patient than in the case of many other diseases. In order to determine whether or not to treat a person who has been bitten we must be able not only correctly to diagnose the presence or absence of the disease in the animal through which the infection was supposed to be transmitted, but to know the possibilities in cases that can only be called suspicious.

Though the incidence of hydrophobia in man is very small compared with that of other fatal affections, the disease is so dreaded, and its results are so terrible, that it needs to be thoroughly understood in order to be able, not only to know and handle it when it does appear, but also to advocate strongly the comparatively simple preventive measures against rabies in the dog which have been shown in certain parts of the world to be so efficacious.

Definition and Synonyms.—Hydrophobia is an acute specific infectious disease of mammals, communicated usually by the bite of an infected animal (chiefly a canine), less frequently by the introduction of the specific virus into a recent wound through contact with the saliva or autopsy material of an infected animal.

It is characterized (1) by a long and variable incubation; (2) by the extremely short course and practically invariable mortality when symptoms develop; (3) by the localization of the virus chiefly in the central nervous system and the salivary glands; (4) by specific pathologic changes in the central nervous system; (5) by symptoms referable to these pathologic changes, that is, first, symptoms of excitation, which may be most pronounced (furious hydrophobia), and, second, those of degeneration, which may be most pronounced (dumb hydrophobia); (6) by being prevented by inoculation with rabies vaccine.

The earliest known name for the disease is "lyssa," which is a Greek word meaning madness. Celsus, in the first century, gave the name "hydrophobia" to the disease in man because of the frequent symptom of fear of water exhibited by man alone. Of course, as the disease has the same etiology in all animals, the name in all should be the same. The Romans called the disease "rabies," meaning furious or raging, or "aquafuga," meaning fear of water. The English call the disease either "rabies" or "hydrophobia," and also speak of "mad animals." In Germany they say *Wasserscheu, Hundswut, Tollwut,* or simply *Wut;* in France it is called *la rage;* in Italy *rabbia;* in Spain *rabia* or *hydrophore.*

"Lyssophobia" is the term used to designate the condition caused by fear of rabies after a non-infected bite. This, of course, is never by itself fatal.

History.—The earliest written records of rabies are said to be found in the writings of Aristotle (about 300 B. C.). In them the statement is made that dogs are subject to rabies, and, when infected, communicate the disease by biting all other animals *except man.* Human rabies was not described in writing until the first century A. D., when Celsus gave what was evidently a compilation; hence the disease in humans must have been known before.

The paralytic form of the disease in dogs was first noted in 1714, and in human beings in 1753. The virulence of the saliva of dogs was shown in 1804, and Gruner (1813) recommended the inoculation of test animals with the saliva of suspicious dogs to determine the diagnosis. In 1821, Magendie and Breschet stated that they transmitted the disease from man to dogs by saliva.

The history of rabies perhaps more than that of any other disease shows how the imagination of people may run wild through lack of knowledge. Though, from time to time, an investigator appeared who showed that he was able to make some true observations, the majority of writers uttered much superstitious nonsense as regards both the origin and the treatment of rabies. For example, some said it was caused by evil spirits and cured by pilgrimages; others that it was caused by fright and cured by self-control; still others claimed that it was caused by a lack of water and cured by very rough sea-bathing, and so on. Even the better observers often recommended empiric and bizarre remedies.

Though the rational treatment by the cauterization of the wounds was among the earliest methods practiced, Razes and others advised keeping the wounds open and suppurating for two months, and Galen recommended extirpating the part bitten when possible.

Even now some people believe that dogs develop rabies because of lack of water, others think that "mad stones" (calculi from the alimentary tract of lower animals) cure, and still others think that there is no such disease—that deaths are due to fright or to something else. Even as late as 1900 the United States Government publishing a circular through Dr. Salmon, Chief of the Bureau of Animal Industry, which gave facts in regard to the reality of rabies, stated that this pamphlet was called forth by the opposition and disbelief expressed by people in letters to the daily press which fostered and encouraged them at the same time by editorials. This disbelief on the part of the people is due to several reasons: first, a reaction against the extravagant ideas that earlier prevailed; second, a sentimentality that refuses to believe so bad a thing of this friend the dog; third, that the few people bitten by mad dogs have so long an incubation and such a low mortality even when they go untreated.

Though we do not yet know the full nature of the cause of rabies, we know more about its etiology than we do about that of several other diseases whose entities are accepted without question. In fact the specificity of rabies has long been proved. Therefore the skepticism which still exists in regard to it is entirely without foundation.

The most brilliant series of experiments to prove the entity of the disease were carried on by Pasteur in the latter part of the nineteenth century. As a result of the first part of his studies he made the announcement to the French Academy in 1884 that he was able to immunize animals against rabies. The principle of his treatment was the same as that demonstrated by him for anthrax, and much earlier by Jenner for smallpox; that is, the production of immunity by inoculations of an attenuated virus. Pasteur's continued studies in collaboration with others and the essential details of his later method, as well as the modifications tried by others, will be given under Treatment.

In the meantime the many efforts made to discover the cause of the disease remained unavailing. Numerous authors from Pasteur down described minute pleomorphic granules in the nerve tissue which they said might be the specific microörganisms, but no growths were obtained in vitro, neither was other evidence forthcoming as to the parasitic nature of these granules. That the cerebrospinal canal with its nerve tissue contents is practically a test tube with living nerve cells as a medium in which the rabies virus grows helped to solve the question of the specificity of the virus, but did not demonstrate its full nature.

Through these studies, however, some facts were learned in regard to the nature of the virus, and in regard to certain microscopic appearances in the central nervous system.

Three of the histologic findings have been made use of in diagnosis: 1 "the rabic tubercles" of Babes; (2) "the areas of spheroidal and oval-celled infiltration" of Van Gehuchten and Nelis; and (3) and most important, the cell inclusions commonly known as Negri bodies, so called after Negri, who was the first (1903) to announce their discovery.

A number of other observers were studying the Negri bodies at the time of Negri's announcement, and many have studied them since, without arriving at an agreement as to their nature. Practically all have come to the conclusion, however, that they are specific for rabies, and so are of great worth in diagnosis (see below).

Geographical Distribution and Prevalence.—Hydrophobia is reported as having occurred with more or less intensity in almost all parts of the world. It is frequent in some of the arctic regions, as well as in parts of the tropics. It is well known throughout most of Europe and many parts of Asia. It is seen in Egypt and all about the Mediterranean. It is said not yet to have been observed in South or Central Africa. Neither has it been reported in Siberia. Australia is said to be free from it because of the rigid carrying out of the six months' quarantine law in regard to dogs. England, because of quarantine and periodic muzzling of dogs, was reported free from the disease for many years before the World War, but in 1918 cases began to be reported again because of the less rigorous quarantine. The disease is common in many parts of the United States.

Kerr and Stimson, in investigating the prevalence of rabies in this country in 1908, found that it had been reported irregularly in all but ten states in the union. In 1911 Stimson stated that it had been reported in all but six states. As the disease is in most sections a non-reportable one, the statistics at present are probably far below the actual numbers. It may be misleading, therefore, to present maps of the incidence of the disease until we have more reliable data (see Seller, 1923).

The number of people bitten, of course, may far exceed the number of animals biting, and the number of animals biting may be greatly exceeded by the number actually affected with rabies. This latter condition is due chiefly to the number of cases of "dumb rabies." Animals suffering from this form of the disease do not usually bite others. But it must not be forgotten that they may occasionally infect man or other animals through contact with their saliva. Rabies, then, may be quite prevalent without knowledge of the authorities. There is no question but that the specific germ of rabies present in the saliva of rabid animals varies in virulence and in quantity in different cases. This no doubt helps to account for the variable number of persons developing the disease after exposure when not treated.

From time to time in the history of rabies severe local epidemics have been reported during which valuable domestic animals have been lost. Then, through extra precautions on the part of the people, the disease has died down again.

Animals Affected.—It is essentially a disease of mammals, though all warm-blooded animals under favorable conditions may be infected. Thus it has been reported very infrequently in certain birds. Those animals that are most often subjected to the bites of canines are most frequently affected.

Neither sex nor age is a direct factor in susceptibility; but in humans more children are infected by bites because more come in contact with dogs in their play; and in dogs more frequent cases occur among animals one to four years of age because these, by their greater activity, run more chances of coming in contact with a stray rabid animal.

The dog is the most frequently affected, probably because he wanders more at large. In countries where wolves are common these animals often stand next to the dog in frequency. In well-settled countries cattle seem to be the next most frequently affected, probably because they stand a greater chance of being bitten by wandering mad dogs. Possibly more cats are affected than is known, since cats often develop the paralytic form of the disease, and therefore the disease may not be recognized.

The following is an average estimate of number and kind of the animals more usually affected. Of course the percentages vary with the different epidemics and in different countries.

Average Estimate of Animals Affected

Canines		Cattle	Cats	Horses	Goats	Sheep	Pigs	Humans
Dogs	Wolves							
85 per cent	Irregular in limited areas	8	5	0.1	1	0.5	0.3	0.04

Other animals, such as deer, foxes, etc., may be infected irregularly, according to the conditions of exposure.

We know little about the natural infection of the species of animals used in the laboratory for diagnostic tests and for the production of vaccine, such as rabbits, guinea pigs, rats, and mice. There is an idea in England that rabbits help to propagate the disease in nature. In this country it is thought in some parts of the West that certain skunks are natural carriers. No proof has yet been given of the truth of these ideas.

Another opinion is that rats and mice are capable of perpetuating the disease without the intervention of the dog. But that they play slight, if any, part in the propagation of rabies is shown by the good results obtained in England and other countries where preventive measures are taken against the dog alone.

Birds seem to have a relative immunity, since old fowls and pigeons, if they take the disease, frequently recover. And if they die their nervous system is said to be innocuous to rats, on subdural inoculation, although it may transmit the disease to other fowls. Their relative immunity may be partly helped by their high body temperature (108° F.).

Only a comparatively small percentage of animals bitten by rabid animals develop the disease. The number is closely proportionate to the intensity and site of the bites.

Cases of developed human rabies are now comparatively infrequent owing to the wide application of the preventive treatment. And the earlier data from which the statistics were compiled were very incomplete. However, we may get a general idea of the percentage of incidence in man after bites, before the Pasteur treatment was established, by the following table of Babes, in which the mortality is arranged in order of site and intensity of bites from different animals.

Percentage Mortality (Babes')

Character and Site of Bites	By Wolf	By Cat	By Dog
Multiple and deep wounds about eye, nose or lips.	100	70	60
Multiple and deep wounds about other parts of face	80	50	50
Multiple and deep wounds on other parts of uncovered body	40	40	30
Single and deep, on finger or neck	20	20	15
Deep, on well-covered parts of body	15	10	3
Superficial, on uncovered parts of body	10	10	10
Same with hemorrhage	2	2	2
Contact of recent wounds with infected saliva	0.1	0.1	0.1
Contact of wounds more than 24 hours old	0	0	0

This gives a general average from dog bites of 24 per cent, which is rather higher than that given by most authors.

In dogs, after dog bite, the average mortality is about 40 per cent.

Bites of herbivora and of man are very slightly dangerous. There are no authentic cases of transference from man. Glands from humans have seldom been found to be infective for test animals.

Seasonal Prevalence.—The disease is not fundamentally affected by the time of the year. If more cases are reported during the summer months the larger number is only apparent or accidental. It may be due to the fact that strays are more frequently seen and more easily caught at this time, because more people are abroad. For the same reason more people may be bitten in summer. This applies particularly to the country. In the larger cities the cases of rabies in the dog are often more frequent during the winter.

Pathology.—It is not known exactly how the rabies germs act immediately after their introduction into the system. Evidence tends, however, to show that they pass chiefly, if not exclusively, along the nerve fibers probably in the surrounding lymph spaces to the brain. Their occasional presence in the blood is only accidental and transient, as the leukocytes in all probability quickly destroy them. Once within the nerve fiber, they seem gradually to develop. They progress so slowly along its course that they do not disturb its function. When the brain is reached they enter the nerve cells, which they first stimulate and then destroy. This process explains all of the symptoms and the pathologic findings.

Gross Pathology.—On autopsy, as might be expected from the action of the organism of rabies just described, no characteristic changes are evident. The fact that no marked changes are found might be considered in itself characteristic.

The central nervous system is often congested. Pin-point hemorrhages and areas of softening may be seen on section. The salivary glands of the dog are also often congested, as are the thyroid, the pancreas, and the suprarenal capsules. Small hemorrhages may also be found in the lungs, and the mucous membranes throughout the body may show catarrhal changes.

The condition of the stomach in the dog has been considered diagnostic, but it cannot be relied upon by itself. This organ frequently has no food particles. It is contracted over a more or less large mixture of foreign substances such as pieces of cloth, hair, leather, wood, and straw. The bile-stained mucous membrane is usually congested and often shows hemorrhagic erosions.

Histologic Pathology.—Many histologic studies have been made of the central nervous system. The first abnormal changes that strike the eye on examining under the microscope a stained section of the spinal cord in rabies are groups of small spheroidal cells surrounding many of the blood-vessels and the large nerve cells. They are especially marked in the anterior and posterior horns. Similar collections of cells are also seen in the white substance along the connective-tissue septa. These cell collections were early described by many observers. Babes (1892) corroborated these findings, called the groups "rabic tubercles," and came to the conclusion after much control study that they were pathognomonic for rabies. But sometimes these groups are not found in cases of rabies; especially are they absent in the early stage; and somewhat similar groupings of spheroidal cells have been found in other forms of disease of the central nervous system. Their use in diagnosis, therefore, is limited.

Many other degenerative changes in the central nervous system were described after this as occurring throughout the course of the disease, but none were found to be absolutely characteristic for rabies. The most important of these changes were found by Van Gehuchten and Nelis (1900) in the cerebrospinal ganglia. In a normal ganglion the large nerve cells are seen lying closely together, inclosed in an endothelial capsule. In a rabies ganglion, on the contrary, many of the large nerve cells have disappeared and their places are taken by groups of small infiltrating spheroidal cells, and by proliferated cells of the capsule.

These changes are found most distinctly and frequently in dogs, least often in man and not so clearly. They may appear quite early; so, while not absolutely specific, they may be of help in diagnosis.

Then came the most important histologic discovery of all—that of the specific cell inclusions called Negri bodies. These bodies will be described under Etiology.

A little later Lentz described certain degenerative cells which he found in "passage" animals, that is, animals which are being inoculated successively with rabies virus, beginning with street rabies. Such cells, however, are seen in other conditions, and are not characteristic of rabies.

The whole process in the central nervous system has been classed as an acute parenchymatous encephalomyelitis.

Etiology.—It was early demonstrated that the saliva of rabid dogs usually contained the specific virus of rabies. Then the virus was shown to be present in the salivary glands. Finally its chief site proved to be in the central nervous system. Any part of the brain or spinal cord of an animal dying of hydrophobia, when inoculated subdurally or intracranially into a susceptible animal, always produces hydrophobia in that animal. Not only this, but very small amounts, that is, very high dilutions of the rabies nerve tissue, may cause the disease, though not with such regularity. This shows that the virus is present in different animals in different amounts.

Inoculations with dilution emulsions of the saliva or the salivary glands do not so uniformly produce hydrophobia. This shows that the sputum does not always contain as many organisms as the brain. The virus is practically always present in the submaxillary glands of dogs, but is not always found in the parotid or the sublingual glands.

In herbivora the glands, and consequently the sputum, are still less regularly virulent. In man they are probably least virulent of all.

Secretions, other than the saliva, of animals suffering from hydrophobia are rarely, if ever, infective. A few investigators have reported that milk may contain some virus, but others have not been able to repeat these results.

This rabies virus, found so abundantly in the nerve substance, has been the subject of innumerable studies. It constitutes a pure culture of the rabies organism. Although the question of artificial cultivation is unsettled, we have learned many facts which are of practical importance in their application to the vaccine treatment of man.

Cultivation of Parasite of Rabies.—Noguchi reports the successful cultivation of the organism producing rabies (hydrophobia). He describes the organisms grown in the cultures as very minute granular and somewhat coarser bodies, some of which resemble Negri bodies, and Noguchi states that they can be transplanted in new cultures through many generations. He says he has reproduced rabies in dogs, rabbits, and guinea pigs inoculated with these cultures.

Williams has raised the question as to whether Noguchi has actually grown the parasite of this disease, or, whether he has not carried over in his cultures some of the original material. His work has not yet been corroborated.

Response of Rabies Virus to the Action of Physical and Chemical Agents.—That this virus is more resistant to certain agents than artificial cultures of many known organisms is thought to be due partly to the fact that it is surrounded by the brain substance which may hinder the action of the agents employed. Poor and Steinhart have considered this. They obtained the virus from the glands by aspiration, filtered it through a Berkefeld filter, and studied the action of certain agents on this comparatively freed virus. They came to the conclusion that the two viruses (brain and gland) are similar in their reactions to the effects of agents tried.

The fact that the virus resists the action of glycerin for a long time has a practical bearing in certain methods of treatment. Glycerin is also used in ridding decomposed brains sent in for diagnosis from contaminating bacteria before making the animal inoculations.

The degree of resistance of rabies brains and spinal cords to different methods of drying and heating has also been made use of in preparing vaccine for treatment. Thus slow drying at a moderate constant temperature (about 20° C.) causes a gradual loss of virulence (see Classic Pasteur Treatment). Very rapid drying at any temperature up to 36° C. preserves much of the virulence (see Harris' Method of Treatment). Under exclusion of air and in a moist condition in the dark the virus preserves its virulence for two months at 23° C., and for twenty-two days at 35° C. It is killed, however, in four hours at 45° C., in twenty minutes at 50° C., and in five minutes at 60° C.

When kept in a cool, dark place, protected from the air, the virus remains virulent for a long time in brains which have become contaminated with many organisms. Thus the decomposed brains of rabid animals after being buried for many months may produce rabies on inoculation into test animals. The brains must, however, be rid of the contaminating bacteria first, either through filtration or by the prolonged action of glycerin.

The action of certain chemical disinfectants on an emulsion (1 to 100 normal salt solution) of fresh rabic brains may be shown by the following table:

ACTION OF CHEMICAL DISINFECTANTS ON EMULSION OF FRESH RABIC BRAINS

Agent	Strength Per Cent	Hours of Exposure	Result
Carbolic acid	1	24	Non-virulent
Carbolic acid	5	20	Non-virulent
Mercuric chlorid	1	24	Non-virulent
Formaldehyd (Cumming)	0.08	2	Non-virulent

The best method for disinfecting rooms, fabrics and so forth is the use of boiling water when possible, otherwise formalin.

Filterability of the Virus.—It has been known since 1903 (Remlinger) that rabies virus, under certain conditions of dilution and suction, passes in part through a Berkefeld filter. Street virus from the central nervous system passes less readily than fixed virus; but gland virus from street cases (dogs) passes most readily of all (Poor and Steinhart).

Negri Bodies.—From the earliest days of the etiological studies of rabies many formed elements have been described as the much-sought-for specific organisms. But each lacked confirmation until Negri and others demonstrated that the structured cell inclusions now known as *Negri bodies* are probably the specific microörganisms causing rabies. They have been made the subject of extensive studies by many investigators, among them Williams and Lowden in 1906. As a result of a series of studies on the nature of these bodies Williams concluded with Negri that they are probably protozoa and the cause of rabies. Williams gave them the name *"Neurorhyctes hydrophobiæ,"* and presented as her reasons for considering them microörganisms the following facts:

1. The bodies show distinct characteristics in both morphology and staining.

2. Their morphology is constantly cyclic, that is, a definite series of forms indicating growth and multiplication can be demonstrated: small, single, rounded or oval plastin-staining granules; similar forms in twos or groups; larger forms containing a definite central or eccentric chromatin mass (nucleus); forms with smaller chromatin masses arranged in a ring about the central mass; evidence of division of these larger forms as well as of the small ones; segmentation of chromatin and distribution of nuclear-staining material throughout the whole organism; division of the organisms into many minute bodies; and finally, from the beginning of the appearance of the smaller masses of chromatin, all stages of budding, a phenomenon which accounts for the appearance in the same cell and at the same time of both large and small forms, and also helps to account for the rapid spread of the organism and for forms small enough to pass certain filters.

3. In rabbit "fixed virus," besides the few larger forms seen by others, very many extremely minute forms are found, within most of which are seen, in well-fixed and stained preparations, a single chromatin granule.

4. With stains such as Giemsa's the lightly basophilic property of the "cytoplasm" of the bodies and the chromatinlike nature of the contained masses and granules are well brought out, better in spreads than in sections.

5. Negri bodies are found in *all* parts of the infectious central nervous system, beginning to appear in the large nerve cells as extremely minute

forms before the beginning of symptoms, that is, on the fourth day in rabbit fixed virus infections and on the seventh day in rabbits inoculated with street virus; thus they are found early enough to account for the infectivity of the host tissue.

Most of those findings have been confirmed. Watson states that he has found in addition sporelike bodies similar to myxosporidian spores. Manouëlian and also Jackson have demonstrated Negri bodies in the ganglion cells of the salivary glands.

Others have brought forward other explanations of the nature of these bodies. All of these hypotheses may be summarized as follows:

1. Negri bodiés are microörganisms and the cause of rabies (Negri, Williams and Lowden, and many others).
2. The plastin-staining portion of the bodies is due to the host cell reaction to the specific microörganisms, which are the small chromatin masses seen within the bodies (Volpino, Babes, Prowazek, and many others).
3. They are due to the cell reaction to the rabies toxin. They may or may not contain the organisms (Marie and others).
4. They are extruded and degenerated nucleolar material (Acton and Harvey).

Something may be said in favor of each of these hypotheses except the fourth; but the balance of evidence seems to us still to be greatly on the side of the first one.

Whatever the nature of these bodies, their practical specificity has been accepted, with the result that all over the world their presence is considered proof that the disease is hydrophobia. The methods for the practical demonstration of these bodies are given under Diagnosis.

Incubation.—The fact that the incubation period in this disease is usually very long is one of chief importance in the treatment of the disease by prophylactic vaccine. It gives time for the long series of inoculations which is considered the best way to produce immunity in the patients bitten.

The time from the bite to the appearance of the first visible symptoms varies usually according to the number, severity, and site of the bites. Rarely is it earlier than twelve days or later than ninety. The limits given are eight days and several years. In most cases of humans it occurs in from three to eight weeks. The statement as to any time over a year must be received with caution. Few cases beyond that time have absolutely reliable data. It is seldom that all sources of possible intercurrent infection, such as contact with the saliva of another animal before it has shown symptoms, can be absolutely ruled out.

The period of incubation varies somewhat (1) with species, being longest in man; (2) with age, being shorter in younger cases, though this may be due to the fact that the younger ones receive more bites; (3) with the site of wounds—the shorter the nerve trunk the shorter the incubation; (4) with the severity of the wounds, in direct proportion; (5) anything that weakens the body, especially the nervous tissue, such as shock, alcohol, syphilis, meningitis, shortens incubation; (6) with the virulence of the strain of infecting virus.

Stimson in 1912 gives the period of incubation in 65 of the cases in man which occurred during 1911 in the following table:

Period of Incubation in 65 Cases in Man

Days	10 to 20	21 to 30	31 to 40	41 to 60	61 to 120	121 to 240	241 to 365	Over a Year
Number of cases.	11	19	9	8	10	3	2	3

Average, 49.25 days.

For lower animals the following table may be accepted:

Incubation in Lower Animals

Animals	Average	Longest	Shortest
Dog	2 to 8 weeks	1 year	8 days
Cat	2 to 4 weeks	1 year	7 days
Cattle	1 to 3 months	3 years	2 weeks
Horse	2 to 8 weeks	20 months	
Swine	2 to 4 weeks	6 months	6 days

Symptoms.—The symptoms in all animals present the same general characteristics and point plainly to the cerebrospinal system as the site of the chief lesions. They may be divided into two groups or stages: (1) those of excitation or irritation; and (2) those of degeneration. If symptoms due to excitation predominate, the disease is called "furious rabies" or "hydrophobia;" if symptoms of paralysis quickly appear, due to rapid degeneration of the nerve centers, the disease is called "dumb" or "paralytic rabies" or "hydrophobia." Many cases present a mixed type of symptoms, and a few are quite atypical.

Some details of the manifestations of the disease as it occurs in the most common biting animal (the dog) may be given in order to help us determine whether or not, in any case, the biting dog is mad and the bitten one needs treatment.

Symptoms in the Dog—*Furious Rabies*—Stage of Excitation.—There may be a slight fever before symptoms are apparent. The first thing noted may be a change of character. A non-affectionate dog may become affectionate and an affectionate one non-affectionate. The increased affection may show itself in more frequent attempts to lick the hands and face of the owner. Even at this time the sputum may be virulent, so we should beware of unnatural playfulness, especially if we know the dog has been bitten. The appetite is variable and may already be abnormal. The unnatural activity and restlessness may gradually become more marked during from two to four days. The animal may appear to have hallucinations, such as seeing imaginary flies and fearing inoffensive objects. Later he loses fear and begins to bite at things and animals, especially at dogs, lastly at man. He may run far away from home in this stage; in fact this is often the first symptom noted by unobservant owners. It is during such runs that he bites people and other animals. He may return exhausted and be quieter for some time. He may even seem normal again; he may recognize his master, respond to caresses, and eat and sleep. Then he again becomes excited. If in a cage he moves constantly. In a room he may bite and tear things. His bark early becomes characteristically altered in pitch and mode. It is described as changing from a succession of resonant sharp barks to a low howl followed by an irregular series of low-pitched barks between unclosed jaws. Some dogs do not bark characteristically; some do not bark more than usual. The majority do not have fear of water; they drink as long as they can, that is, until local and general convulsions are marked. The saliva drops, but the animal may not "froth at the mouth."

Stage of Paralysis.—The first stage passes insensibly into the second. Signs of weakness of certain muscles appear, often in the posterior extremities, sometimes in the anterior, and sometimes in the muscles of the jaw or other muscles of the body. The local and general tonic-clonic spasms gradually become less. The pupils are dilated. Respirations and heart beat are irregularly increased. Paralyses increase and death finally supervenes. The duration of obvious symptoms is usually from four to six days, not infrequently seven to eight days, practically never over ten days. The stage of irritation is from three to four days; the stage of paralysis is from one to two days.

Dumb Rabies.—Fifteen to 20 per cent of cases among dogs occur in this form in nature (Högyes). The stage of excitation may be so short as to be unnoticed. Paralysis may be the first symptom observed, often first in the lower jaw, causing "drop jaw," which makes the owner think that his dog has "a bone in its throat." The animal does not bite any one when suffering from this type of the disease, but its sputum may be as virulent as that of a biting animal, and may cause rabies if it comes in contact with any recent wound, even that produced by a hangnail. The posterior extremities and the rest of the body quickly become paralyzed. Paralytic rabies is said to be a more intense form of the disease, but that this is not so in certain cases seems evident both from the clinical history and from the amount of infective material found in the central nerve system and in the salivary glands. We have had several cases of drop jaw which have lasted a longer time than the other forms of the disease.

Poor says that he has seen a few cases of drop jaw of uncertain origin which have become well. Whether or not these are spontaneously cured cases of rabies we cannot say.

Symptoms in Man.—The psychic and reflex symptoms, which are usually the first to appear, are similar to those following any excitant, causing hypersensitiveness of the nerve cells; therefore they may be easily simulated. But one is not left long in doubt. Sometimes the first symptom is a local irritation of the wound, a tingling and itching, accompanied by some engorgement and pain. This may be simulated by neuralgic pains from any cause. Sometimes the patient complains of a sensation of constriction in the throat, or of difficulty in walking or breathing, or of precardial anxiety, or of neuralgic pains in other parts of the body. There is usually a moderate rise in temperature (38° to 39° C.). These indefinite symptoms generally last about forty-eight hours. During this time one of the most characteristic symptoms in man, the fear of water, may develop. It is not always marked. It is simply due to the painful spasm of the muscles of deglutition from the attempt to swallow. Of course the more the patient feels he cannot drink the more thirsty he becomes, hence the reason why the greatest fear seems to be of water. Solid foods are more readily taken than fluid. There is a characteristic pharyngeal and respiratory spasm on exposure to a draft of air (aërophobia). Loud speaking may also cause spasms (hyperacusia). Remissions, which may give the friends short hope of recovery, usually occur, except in the very severely infected cases. At about forty-eight hours the periods of excitement become more marked. There may be hallucinations, and even mania; but there is seldom a tendency to injure others, even by biting. The patient realizes between the attacks what he has done. Indeed, his mind is irregularly clear until near the end. His voice becomes hoarse with a peculiar quality. There is never any real barking, though sometimes the noise the patient makes slightly simulates it. The eye symptoms are photophobia, nystagmus, and sometimes strabismus. The pupils are unequally dilated.

Vomiting is frequent, and may be dark-colored as a result of hemorrhage or regurgitated bile, or both.

During this stage death may occur suddenly after one to four days' illness, due to apoplexy or asphyxia, or after a short period of apparent agony. But usually the patient passes into the paralytic stage.

Paralytic Stage.—The muscles relax, the jaw drops, ropy saliva flows, the face becomes smooth and expressionless, the patient becomes comatose, breathing becomes irregular and feeble and finally stops. The temperature increases just before death; it may be as high as 44.5° C. The pulse is generally irregular and over 100. Just before death the blood shows a leukocytosis. Sugar and acetone may be found in the urine, but no albumin. This stage lasts from two to eighteen hours.

Paralytic Hydrophobia (*Dumb Rabies*).—This type of the disease, which includes those cases that show almost from the beginning symptoms pointing to degeneration of the nerve tissue, is less recognized in man than the former type, and probably has been sometimes incorrectly diagnosed.

From the standpoint of treatment its recognition is necessary in order to be able to differentiate it from the paralyses which occur occasionally during or just after Pasteur treatment.

Though this form of the disease was described long before the Pasteur treatment came into use, it had been forgotten, and when cases occurred after the treatment many people said that Pasteur gave the disease instead of curing it. The proof of the relation of the disease to street rabies, rather than to laboratory rabies, in these cases is given by animal inoculations.

The onset in humans is the same as that of the convulsive type, but shorter. Then the lower extremities feel heavy and numb. They become quickly ataxic and then paralyzed. The paralyses spread irregularly. Death occurs usually from heart paralysis in from two to eight days. Consciousness is retained until late in the disease.

Diagnosis.—In man rabies must be differentiated from hysteria or lyssophobia, from delirium tremens, from tetanus, and from the action of several poisonous drugs.

The history of the case must be determined if possible. A negative history with the absence of reflex irritation to stimuli, especially to air, will usually eliminate rabies.

The following points should be considered in history-taking: (1) exposure to infection from the biting animal and exposure of this animal to infection; (2) length of incubation in each; (3) symptoms; (4) termination; (5) postmortem finding; (6) inoculation tests in animals.

In hysteria or lyssophobia the reflex response to stimuli is never so intense as in rabies, and the symptoms are amenable to suggestion.

In tetanus the spasms are tonic, with continued contraction of the jaws instead of alternate relaxation.

In the dog a positive clinical diagnosis can usually be made by an experienced doctor if the animal can be under prolonged observation, but the animal so frequently is killed on sight that this sure diagnosis can rarely be given. So we must usually rely upon the laboratory tests. These are two in number, namely, the microscopic examination and the inoculation of test animals.

Since the discovery and proved specificity of the typical Negri bodies their demonstration has been considered positive evidence of rabies.

Williams, in 1904, recommended a rapid spread method for demonstrating these bodies which allows a diagnosis to be made in a few minutes. This method was later perfected by Williams and Lowden, Van Gieson, Frothingham, Harris, and others, and is now made use of for rapid diagnosis in most parts of the world. We have used the spread method for showing the presence of these bodies since 1904, and we still find it eminently satisfactory. We can still state that we have never obtained negative results from inoculating animals with material that shows typically structured Negri bodies. We must say, however, that we continue infrequently to receive brains that do not show these typical bodies, yet on animal inoculation produce rabies. All of these brains, it is true, show suspicious small forms, and a few of them if kept at 12° to 18° C. overnight show typical bodies the next day. So the percentage of failures by the spread method is very small. Of course decomposing brains, which unfortunately are sent for diagnosis quite frequently in the summertime, cannot always be diagnosed successfully by this method. In these cases, and in the few suspicious cases, animal inoculations must still be made as the final test of the presence of rabies. Sections are recommended by some workers, but in our hands they have not given as much aid as the spreads.

In certain cases when animals are killed too early in the disease to give time for the general development of the organisms in the brain, the salivary glands may be virulent. It has been shown that the sputum may be virulent many days before the appearance of brain symptoms. The longest time reported is eighteen days. In such cases, of course, contact with another rabid animal must be absolutely excluded.

The following is the routine method in the New York City Health Department of handling the material sent in for diagnosis:

1. If the material is fresh, spreads are made by pressing between a glass slide and a coverglass a small, thin section of the gray matter from each of the following parts of the brain: (a) the cerebral cortex, (b) Ammon's horn, (c) the cerebellum. The material is spread along the slide by moving the coverglass down with the finger. Experience teaches the amount of pressure to be used.

2. When partly or completely air-dried the smears are fixed for about ten seconds in neutralized [1] methyl alcohol (C. P.) to which 0.1 per cent of picric acid has been added. The excess of the fixative is removed by blotting with fine filter paper.

3. The fixed smears are stained in the following solution:

Saturated alcoholic solution of fuchsin	0.5 part
Saturated alcoholic solution of methylene blue	10.0 parts
Distilled water	30.0 parts

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[1] The wood alcohol is neutralized by adding sodium carbonate, about 0.25 gm. to 500 c.c. of the alcohol.

This solution, which is a modification of the one proposed by Van Gieson for staining the Negri bodies in smears, changes rather quickly at room temperature, but, kept in the ice-box, it gives good results for an indefinite time. The stain is poured on the smear and held over the flame until it steams. The smear is then washed in tap water and blotted with fine filter paper.

With this stain the Negri bodies appear a magenta color with blue granules, the nerve cells blue, and the red blood-cells yellow or salmon color.

Giemsa's stain gives brilliant results, but it requires more time than the above stain, and therefore is not good for diagnostic work. In our experience the other published methods of demonstrating these bodies possess no advantage over the first one given here.

4. If nothing is found smears are made from various other parts of the brain.

5. If still nothing is found an emulsion is made in 10 c.c. normal salt solution of pieces the size of a bean from the different parts of the brain, and an intracerebral inoculation (¼ c.c.) is made into each of three guinea pigs. If brain is contaminated emulsion is filtered through porous candle.

6. Pieces of the brain are also put into sterilized neutral glycerin for later inoculations, if for any reason the first should fail. Brains so preserved remain active in the ice-box for over three months. By this method contaminated brains lose many of their extraneous organisms.

7. An emulsion made from the contaminated material preserved in glycerin is inoculated after two weeks, unless positive results have been had from the first inoculations.

8. If the brain is very soft, sections may be made, but usually this is not necessary.

Treatment.—The treatment of hydrophobia is essentially one of prophylaxis by means of a specific vaccine. Until recently, serum has played a very small part in the treatment and drugs none at all, except in alleviating the symptoms of the developed disease.

Philips, Berry, and Snook have given a good summary (1921) of our knowledge concerning the question of recovery from rabies.

Prophylactic Treatment.—The prophylactic treatment may be considered under two heads, local and constitutional.

Local Treatment.—The wound should be cleaned immediately with any fluid antiseptic solution, and then be cauterized with fuming nitric acid. Prompt cauterization may be very effective. Fuming nitric acid has been found to be better than any other chemical cautery. The acid should be applied on the point of a tapered glass rod, or drop by drop from a capillary pipet so that the amount may be carefully controlled.

Contact with bony, cartilaginous or bloodless parts should be avoided if possible. To these parts apply pure carbolic acid and the fuming nitric acid to the other tissues adjacent. These tissues heal well after the use of nitric acid. The actual cautery is effective as far as it reaches the parts of a wound, but fuming nitric acid, being a fluid, reaches the deep crevices which the hot iron may not touch. The use of pure carbolic acid, iodin, silver nitrate, etc., in wounds made by rabid animals, have but little value as compared with fuming nitric acid.

Constitutional Treatment.—This consists chiefly in the use of the specific vaccine. If we could determine easily in each case the presence of rabies in the source of infection, the procedures as to treatment would be comparatively clear-cut. Unfortunately there are several factors which interfere with an immediate and definite decision: (1) the biting animal may be a stray which has disappeared after the biting; (2) it may be an apparently healthy animal; (3) it may have indefinite symptoms; (4) it may have been killed before clinical or microscopic manifestations appeared; (5) it may be sent to the laboratory without a history and in too bad a condition for microscopic diagnosis.

If we cannot rule out these factors we cannot rule out rabies, and unless we can rule out rabies we should be guarded in advising no treatment, especially in communities where cases of rabies have been reported.

The antirabic treatment should be advised, therefore, when any of the following conditions obtain:

1. When the animal shows clinical or microscopic signs of rabies.

2. When the animal has disappeared just after biting and cannot be found. This in itself is a suspicious symptom, especially if the animal is a stray. All efforts, however, should be made to obtain further facts in regard to the appearance and actions of the animal. The apparent reason for the bite and the successive biting of other animals or people must also be borne in mind, as well as the fact that the bitten person's imagination may be colored by the wrong ideas of the disease that are so common among the laity.

3. If the biting animal has been killed before it can show microscopic evidence of rabies, or if its brain is sent to the laboratory in too bad a condition for immediate diagnosis, and if the bite is severe and unprovoked, beginning treatment should be advised pending the results of inoculating test animals. If these test animals show no symptoms in fourteen days the treatment may be stopped; if the animals show symptoms later the treatment may be started again and the whole course finished.

4. If an apparently healthy animal or one with only slightly suspicious symptoms should bite a person, the advice should be to *keep the animal under observation for at least three weeks,* and to begin treatment

if suspicious symptoms appear or become more marked. It will be remembered that the longest period between the biting and the appearance of symptoms during which a dog's sputum has been shown to be virulent is reported to be eighteen days.

5. If the animal is killed and no evidence can be had for or against rabies, treatment should be advised in areas where rabies is prevalent.

6. When patients have been only exposed to an animal's saliva, treatment should be advised unless we can absolutely rule out fresh cuts or abrasions on the parts exposed.

Probably all of those cases where rabies is said to have developed without bite or contact are in reality contact cases. The slightest fresh abrasion from whatever source may be more dangerous than deeper clean-cut wounds which bleed freely; such abrasions may be more easily overlooked.

Specific Treatment.—The specific or antirabic treatment of hydrophobia in man dates from 1885, one year after Pasteur had made his first announcement to the French Academy of the results of his extensive studies on this disease. In this year Pasteur, with Roux and Chamberland, gave the results of further experiments on methods of obtaining a less virulent virus for use in beginning protective inoculations. The method which they recommend became known as the Pasteur Method, and with certain modifications it has been and still is used all over the world.

"Street Virus" and "Fixed Virus."—In Pasteur's first attempts to immunize against rabies certain difficulties were encountered, chief among which were: (1) the inability to obtain non-variable inoculation dose, owing to the irregular strength of the virus as it occurred in nature ("street rabies"); (2) the inability to obtain a virus surely attenuated that would produce immunity and still be harmless.

To overcome the first difficulty, that is, to get a virus that would always produce rabies in essentially the same dose, Pasteur tried passing the virus successively through different species of animals by subdural inoculations. He found by this method that in certain animal species (for example, monkeys) street virus became attenuated, while in others (notably rabbits) it became markedly increased in virulence, as evinced by the shortened incubation period. The attenuation in virulence by passing through less susceptible animals occurred much less regularly than the increase in virulence by passage through more susceptible species; therefore he discarded the passage method of attenuating the virus, but continued working to increase the strength. He found that after many passages through rabbits (about 50) the virus present in the central nervous system (the medulla was mostly used) of the rabbits dying from the infection would, when inoculated into a fresh rabbit, bring it down with the disease in a fixed time. He called this virus "virus fixe" (fixed virus), and used it as the basis for further operations in preparing his vaccine treatment. He found a way to attenuate this virus more or less regularly by drying and so to obtain gradually increasing doses up to the fully virulent virus. He also found that this rabbit-fixed virus did not so often cause death in animals when given subcutaneously as did street virus. Later others found that by inoculating themselves subcutaneously with emulsions of fully virulent fixed virus no ill effects were produced, at least in some human beings, by this method of inoculation.

Högyes states that he obtains a fixed virus sooner (in 16 passages) if he uses only young rabbits. Babes claims that many strains of street virus will become fixed for the rabbit by three to four preliminary passages through the guinea pig.

The strain of fixed virus in one institute may differ slightly in strength from that in another.

Babes gives the following table of loss of virulence by drying in fixed virus cords of different institutes:

Paris and St. Petersburg	cords	become	non-virulent	in	5 to 6	days
Bucharest	“	“	“	“	4	“
New York and Moscow	“	“	“	“	6	“
Kiev, Sartou	“	“	“	“	6 to 7	“
Tomsk	“	“	“	“	9	“

The various steps in the classic Pasteur treatment may be summarized briefly as follows: (1) obtaining a fixed virus by successive passages of street virus through a rabbit; (2) removing aseptically the spinal cords of rabbits dying from such fixed virus infection and drying the cords over caustic potash at 20° C. (70° F.) in order to attenuate the virus until no virulence is shown in test animals (from eighth to tenth day, according to Pasteur); (3) inoculating patients subcutaneously on successive days with emulsions from measured quantities of these cords, beginning with the dried avirulent cords and passing to the infective ones until fully virulent material is given.

Pasteur began his inoculations with a fourteen-day cord, and carried the treatment on for eighteen days in the lighter cases and twenty-one days in the more severe ones. His schemata are given below.

Modifications of Pasteur's Method.—Pasteur's method in its entirety was soon adopted in many lands, and his results were corroborated. Before long, however, a number of modifications were suggested by different observers; some of these modifications were slight, others more fundamental. Some have been widely used, such as Högyes' dilution method; others have had a limited application in lower animals and are probably only of theoretic interest in regard to man. Such are the intravenous inoculation of brain emulsions from street rabies into herbivora (Nocard and Roux, Protopopoff), and the intraperitoneal inoculations of large doses of fully virulent fixed virus into dogs, cats, or rabbits (Hellmann, Heim, Remlinger). Immunity has been produced also in rats by allowing them to feed on rabid brains (Fermi, Repetto, Remlinger). Negative results have been reported in other animals by this method.

Högyes in Budapest was one of the first to use a different procedure. He claimed that the virus by Pasteur's method was attenuated only through the death of some of the specific organisms, that is, that there were simply fewer living organisms in the early doses than in the later and that, therefore, the same result might be obtained with even more accurate dosage perhaps by giving gradually decreasing dilutions of a fresh virulent cord. By diluting sufficiently he obtained a mixture which when inoculated did not produce rabies in the test animals, a result similar to that following an eight to ten-day dried cord. This dilution he used for the first inoculation and gradually stronger dilutions for the succeeding ones. In this way Högyes says he has produced immunity in dogs even to intracranial infection.

Fig. 1.—Inoculation of Rabbit for Production of "Fixed Virus."

Some workers question the similarity of the two methods. They claim that by the former method the dead bodies or other toxins of the rabies germs contained in the dried cords are able to produce a certain degree of immunity. Poor in our laboratory produced immunity by the inoculation of nine, ten and eleven-day cords. But such cords probably always contain a few living germs—not enough, however, to cause death.

Other methods of attenuating or diluting fixed virus have been used, such as exposure to the action of heat, cold, gastric juice, glycerin, or carbolic acid.

The mixed treatment with specific serum and vaccine has also been employed chiefly by Marie, by Remlinger, and by Babes. It is not used is this country.

Some details of the more important of these methods with the number of cases treated by them, the percentage of mortality, and the complications will be considered. *In making up statistics for mortality from rabies we must always consider the time allowed for the establishment of immunity by the treatment.* This has been found to take place in about fifteen days after the last inoculation. Any deaths that occur within fifteen days after treatment is finished are considered to have been too severely infected or too susceptible or infected with too virulent a virus to have given time for the production of immunity by the treatment. Therefore, two figures should always be given in mortality statistics: the absolute mortality and that occurring beyond the fifteen-day limit (corrected mortality). Dr.

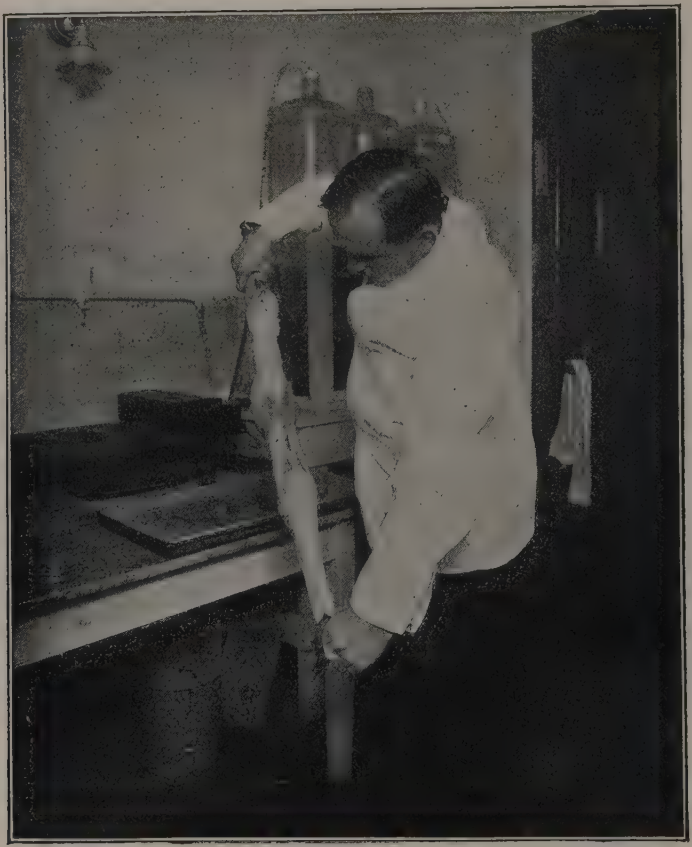

Fig. 2.—First Step in Removing Fixed Virus Spinal Cord from Rabbit. Muscles bared by pulling skin over head.

D. W. Poor has kindly given valuable assistance in preparing the following descriptions.

Methods of Attenuation by Gradual Drying.—The method of drying the cords slowly at a moderate heat is the classic method of Pasteur. It has undergone modifications in three general directions: (1) lengthening or shortening the period of treatment; (2) starting the inoculations with a less attenuated cord; (3) increasing or decreasing the amount given at each injection. The method of drying the cords, however, has remained essentially the same as that used by Pasteur.

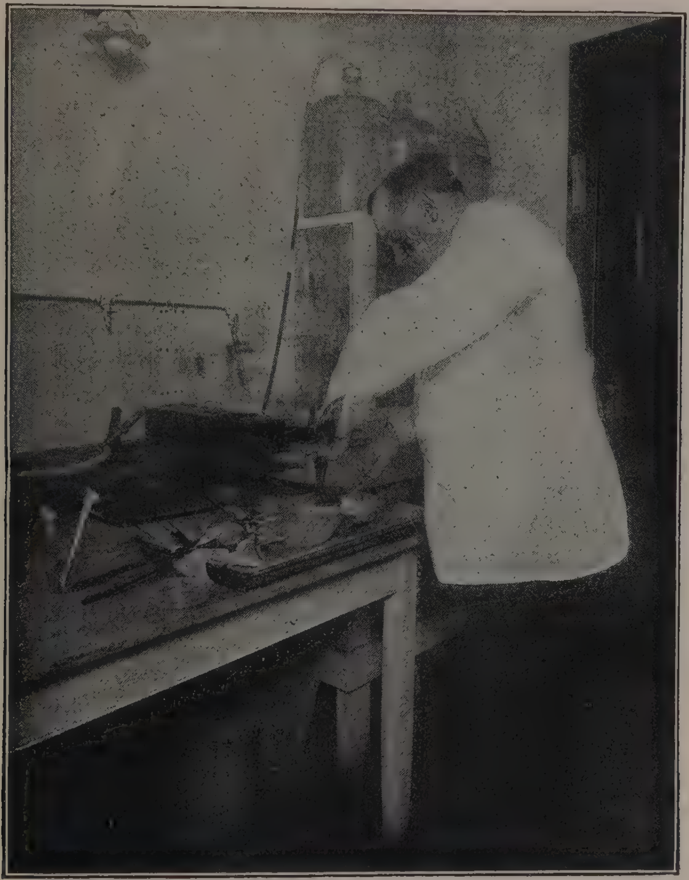

FIG. 3.—SECOND STEP IN REMOVING FIXED VIRUS CORD FROM RABBIT. The cord is pushed from its canal by a long wire probe and lies curled on the sterile muscles of the neck.

The rabbits are inoculated for the production of "fixed virus cords" as follows:

The animals may be etherized, but, if the skin over the point of the cut be washed just before the operation with 5 per cent carbolic solution, the very slight pain from the skin cut necessary is deadened by the anesthetic action of the carbolic acid. The rest of the operation produces no pain. A one-fourth inch incision through the skin is made back of the eye on one side of the median line, the skin is held apart and a small opening is made with a stylet through the skull bone just large enough to admit the fine short (¼ inch) hypodermic needle of the syringe containing the emulsion (0.2 c.c.) to be inoculated (Fig. 1). The inoculation is made intracerebrally. When the needle is withdrawn the skin is allowed to come together, and, though no further treatment of the wound is necessary, it is usually covered with a little cotton and collodion.

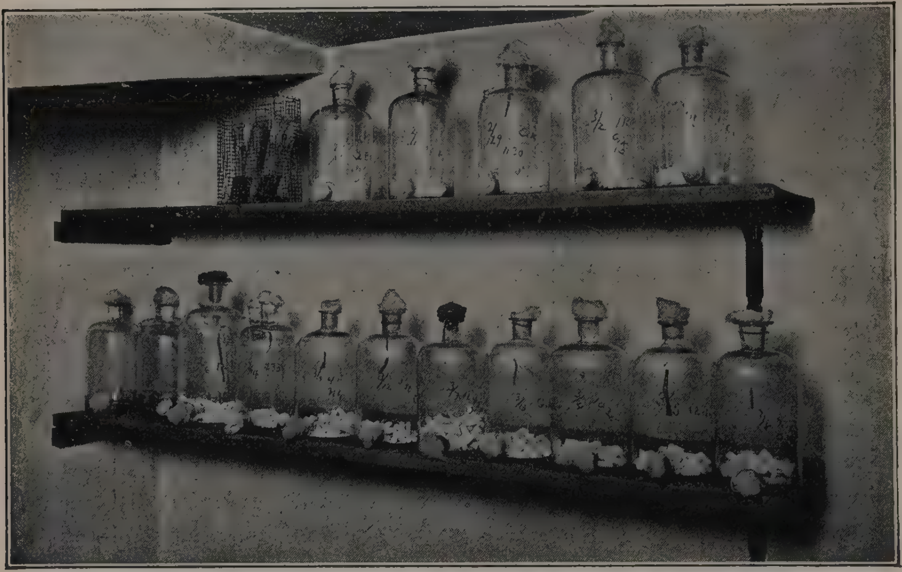

Fig. 4.—One Corner of Constant Temperature Room Showing Drying Bottle Containing Fixed Virus Cords Being Prepared for Vaccine.

The cord is removed by a modification of the method of Oshida in the following manner: Strict asepsis is preserved. The rabbit when completely paralyzed (seventh day) is killed by gas or chloroform and is dropped into a 5 per cent solution of carbolic acid for five minutes. It is then removed, the excess of carbolic solution is drained off, and an incision through the skin at the upper and inner part of the thigh is made. The skin is loosened by cutting around the lower portion of the trunk. It is then pulled by the hands toward the upper extremity of the animal and over the head to the ears, leaving the back exposed and sterile throughout the entire length of the spine (Fig. 2). The spine is then divided transversely near each extremity by bone-cutting forceps after the muscles have been cut through about these areas so the spine may be more easily reached. With a long wire probe swabbed with cotton at one end the cord is pushed upward from its canal, freed from its nerves and membranes. The spine is steadied by lion-jawed forceps. The cord curls in a spiral as it emerges and rests on the sterile muscles of the neck (Fig. 3). It is lifted with forceps placed in a Petri dish and cut in two. A small piece is cut from one end and is dropped into a tube of broth to test its purity. A ligature with one long end is placed about each piece, both of which are then hung in a drying bottle (Fig. 4).

Drying the Cord.—The drying bottles are sterile aspiration bottles with both openings plugged with cotton. A one-inch layer of sticks of caustic potash covers the bottom, and the pieces of cord are suspended from the top cotton plug by their attached ligatures. The bottles are then labeled and placed in the constant temperature room (Fig. 4) or incubator, which is kept at a temperature of about 21° C. (70° F.). After twenty-four hours' drying the cord is known as one-day cord; after two days, as two-day cord, etc. Pieces of cord cut off at any time and put into glycerin will retain about the same strength for several weeks. This procedure is followed in regions where there are few cases of rabies, and the daily killing of rabbits to keep up the vaccine would be a large expense. It may also be followed where treatment is sent by mail.

The schemata devised by Pasteur which have been most used may be tabulated as follows:

PASTEUR SCHEMATA FOR DRYING THE CORD

Days		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Light Cases	Age of Cords	14 13	12 11	10 9	8 7	6 6	5	5	4	3	5	5	4	4	3	3	5	4	3			
	Amount c.c.	3 3	3 3	3 3	3 3	2 2	2	2	2	1	2	2	2	2	2	2	2	2	2			
Severe Cases	Age of Cords	14 13 12 11	10 9 8 7	6 6	5	5	4	3	4	3	5	5	4	4	3	3	5	4	3	5	4	3
	Amount c.c.	3 3 3 3	3 3 3 3	2 2	2	2	2	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2

The New York City Health Department used the same plan with slight modifications up to January, 1906, when they began treatment with a ten and nine-day cord and finished with a two-day. They continued with this until August, 1913. Since then they have been using one of the more intensive methods first adopted by the Berlin Institute. From 1906 to 1921 inclusive they treated 6,738 cases infected by rabid animals, with a total mortality of 0.47 per cent and a corrected mortality of 0.17 per cent. They have had 7 cases of definite paralysis with 2 deaths. Over 11,000 cases in all were treated during this time, including those not bitten by rabid animals.

Since it had been found that fresh rabbit fixed virus inoculated subcutaneously into man is probably harmless, the Berlin Institute, with the hope of obtaining an earlier immunization and a shorter treatment, began to give still earlier cords. In 1901 it began with the eighth-day cord on the first inoculation, and was inoculating a two-day cord on the eighth day of treatment. Its treatment lasted twenty-one days. This method was adopted at the Hygienic Laboratory in Washington in 1908, with slight variations for the different degrees of bites.

Modifications Used by the New York City Health Department (Fielder)

Cord Dried	Scheme 1	Scheme 2	Scheme 3
	Jan. 1, 1912, to Aug. 2, 1913	Aug. 3, 1913, to May 6, 1914	May 7, 1914, to Dec. 31, 1921
	Number of Injections in 21 Days	Number of Injections in 21 Days	Number of Injections in 21 Days
Ten days	3	0	0
Nine days	3	0	0
Eight days	1	1	2
Seven days	1	1	2
Six days	1	1	2
Five days	1	2	2
Four days	5	5	9
Three days	5	7	8
Two days	5	8	0
Number of patients treated	1,408	811	3,163
Cases of paralysis.	1	6 (one fatal)	0
Cases of rabies....	4	2	10 (7 within 15 days after completion of treatment)

Thus it will be seen that Scheme 2 is somewhat stronger than Scheme 1, since it contains three more injections of two-day cord, and much stronger than Scheme 3, which includes nothing more active than three-day cords. Scheme 2 is very similar to the one employed by the Hygienic Laboratory of the United States Public Health Service, Washington, D. C., and by most of those who produce antirabic vaccine in this country, with these differences: (1) the amount of cord per dose was only two-thirds of that employed in the Washington scheme; (2) we used a two-day cord instead of one-day cord on the eighth and twenty-first days of treatment.

Treatment by Mail.—The New York City Health Department was the first to send out treatment by mail to physicians for their own patients. Full directions are sent in the mailing case. One-fourth per cent of carbolic acid is added as a preservative to the emulsions prepared as above for all treatments. The Washington Hygienic Laboratory soon began sending treatment by mail, and recently manufacturing firms have followed suit. The results from the treatment sent in this way seem to be equally as good as those from the treatment administered at the laboratory.

More Intensive Treatment.—In Berlin, where intensive treatment has been longest used, they began to employ even fresher cords for beginning doses because they continued to have late deaths, though not quite so often, after the more intensive methods they were using. Since 1910 Joseph Koch, the present chief of the Institute, has been using the following schema:

Koch Schema

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Age of Cords	3	2	1	1	3	2	1	1	3	2	1	1	3	2	1	1	3	2	1	1	1

The dose is 2 c.c. of cord emulsion (1 part of cord in 5 parts of sterile physiologic salt solution) inoculated once a day into the subcutaneous tissue of the abdomen. Children and adults receive the same dose.

Simon gives the following statistics of the results of Berlin's increasingly intensive methods:

Berlin Statistics

Period	Age of Cord Used for Beginning Inoculation	Cases	Paralyses	Mortality	Per Cent
I. 1898-1906	Chiefly 8-day cord	2,896	0	21	0.7
II. 1906-1900	4-day cord. Sometimes 3-day cord	1,490	2	7	0.47
III. 1909-1910	3-day cord for all cases	819	3	5	0.6

Several other institutes are employing very intensive treatments, but their cases are still too few for consideration.

Some directors still use the older methods on the whole and even prolong the treatment. Remlinger, for example, begins with the nine-day cord, and ends in eighteen to thirty days, according to the intensity of the bites.

Rapid Drying of Rabies Virus.—Harris developed a new method of drying rabies virus and of regulating the dosage.

Technic.—The brain and cord are removed aseptically and ground up in a sterile mortar with a sufficient quantity of CO_2 snow thoroughly to freeze the tissue. The frozen nerve tissue and snow are then placed in a Scheibler jar over H_2SO_4, the jar being kept in a frigo apparatus. A vacuum of from 5 to 2 mm. is produced in the jar, which is then kept at the temperature of 18° C. by an ice and salt mixture for a sufficient length of time to dry thoroughly the nerve substance, which then appears as a dry powder. About two days are required for one brain and cord which lose about one-half of their virulence in the process. The powder is then sealed in tubes in vacuo and kept at a temperature below 0° C. until required for use.

It has been found that by keeping the powder thoroughly dry and cold practically no further loss of virulence occurs for at least six months.

Before storing the virus for use its strength in units is computed, the unit being the minimal infecting dose (M. I. D.) for a rabbit when injected intracerebrally.

The advantages claimed for this method are: (1) the ease and economy with which a large amount of virus can be prepared, it being necessary to prepare the virus for use even in large laboratories only at intervals of several months; (2) the possibility of more accurate dosage for the patients; (3) a shortened period of treatment; and (4) the inoculation of more virus units.

The required amount of powdered virus is weighed out each morning, and the necessary dilutions in salt solution for the various patients are made from this.

D'Aunoy has recently given a detailed description of this method with some modifications and results of its application. Several thousand cases have been reported treated according to this method. The results have been uniformly good. No cases of paralysis have occurred.

Fixed Virus Attenuated by Heat.—This method was first used by Babes in Roumania, and it is still a part of the complicated Roumanian method. It has been used since 1896 by Puscariu, of Jassy. Simon, who reports personal communications from Puscariu, divides the latter's methods of treatment into three periods.

1. From 1891 to 1896 Babes' modification of the Pasteur treatment was used. Six hundred and thirty-one cases were treated, with 7 deaths.

2. From 1896 to 1901 Puscariu's technic was employed, which was as follows: The brain of a rabbit infected with fixed virus was ground up with 100 c.c. normal salt solution in a sterile mortar and strained through a fine sieve. It was then placed in test tubes and heated in a special water bath for fifteen minutes at different temperatures for the different days. During the above period the emulsions were heated from 80° to 45° C., the dose was 2 to 3 gm. daily, and two injections were given each day.

The duration of the treatment was from twelve to twenty-one days.

Two thousand six hundred and thirteen cases have been treated, with 10 cases of paralysis and a mortality of 0.4 per cent.

3. From 1901 to the present time a less intensive scheme has been used. The emulsions heated from 80° to 70° C. have been omitted, and only one injection each day has been given. In 1912 Puscariu reported

that 3,000 cases had been treated by the above scheme, without a death from rabies and without a case of paralysis.

The schemata of heating used in this present method at Jassy are as follows:

Jassy Schemata of Heating

Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Light cases	65°	60°	55°	65°	60°	55°	50°	45°					
Medium cases ..	65°	60°	53°	63°	60°	55°	50°	60°	55°	50°	45°		
Severe cases ...	65°	60°	55°	50°	50°	55°	50°	45°	60°	55°	50°	43°	Fixed virus

As long as we do not know the site and severity of the bites, the time intervening between bites and beginning treatment, the diagnosis of the animals biting, and other details mentioned farther on, we cannot judge how much these results mean.

It has been claimed by others, judging from the earlier results obtained with the heat method, that this treatment produces more cases of paralysis. Babes himself says that he had more cases of paralysis, but fewer cases of death.

Other Methods of Attenuating the Virus for Dosage.—The methods by partial digestion and by bile have been recommended, but have not been used to any extent in practice.

Attenuation by Glycerin.—Calmette recommends for beginning inoculations a fixed virus cord that has been kept in glycerin until it has lost its virulence (from three to five months). The method of preserving in glycerin the cords dried by the Pasteur method has also been used. This is advantageous in small institutes with few patients. This method is also used to send treatment by mail.

Attenuation by Carbolic Acid.—Fermi, of Sarosarsi, began using the following method in 1900: A 5 per cent emulsion of fixed virus in normal salt solution is sterilized by 1 per cent carbolic acid. Three c.c. are given each morning and each evening over a period of from twenty-five to thirty days. Between 1900 and 1908 1,053 persons were treated, with 2 deaths. Since 1907 Fermi has used a serum-vaccine mixture, but not according to Marie's method. The carbolized vaccine and antirabic horse serum are mixed in equal amounts and allowed to stand for an hour. Three c.c. are injected daily.

In 1921 Umeno and Doi reported that they had succeeded in protecting dogs for at least a year from rabies by the inoculation of one dose of a vaccine killed by the prolonged action of carbolic acid. As a result of this work ordinances have been made in certain parts of this country to vaccinate all dogs each year before licenses are granted.

Fixed Virus Modified by Dialysis.—Cumming, of Ann Arbor, has devised a method of antirabic vaccination, in which he uses fixed virus which has been rendered avirulent by dialysis. The emulsion of fixed virus is placed in collodion sacs (prepared by the Novy method and sterilized in the autoclave at 105° C. for twenty minutes) and dialyzed in distilled water for from twelve to twenty-four hours. The resulting vaccine does not produce rabies on intracranial inoculations, but does produce immunity on subcutaneous inoculations. Experiments by Cumming on rabbits show that whereas the original Pasteur method protects against only twice the minimum lethal dose (minute directions for obtaining the M. L. D. are given) injected intracerebrally, and the Högyes method against one and one-half times the fatal dose, the dialysis method protects against at least three times the fatal dose. He also claims that immunity is produced at an earlier date than by the other methods. Treatment (2 c.c. of the vaccine) is given daily for from fifteen to twenty-five days. Cumming reports over 800 cases (62 per cent bitten by animals proved to have been rabid) treated without a death and without complications.

Poor, experimenting on animals with this method, reports results comparing favorably with those of the Harris method.

Method in Which Fresh Fixed Virus Is Used for Inoculations—*Doses Regulated by Dilutions—Högyes' Method.*—The brain of a rabbit dying after fixed virus infection is rubbed up with 100 parts of a 0.7 per cent salt solution. This is the original mixture from which the dilutions to be used in the inoculations are made. These dilutions are 1 : 200, 1 : 500, 1 : 1,000, and 1 : 2,000. The doses given are 1½ to 4 c.c., which represent 0.001 to 0.04 gm. of cord. According to Simon, the schemata of Högyes' method, which at first were more complicated, may now be condensed as follows:

Condensed Schemata of Hogyes' Method

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Slight cases—children	0.001	0.002	0.003	0.004		0.005		0.0075		0.01		0.015		0.02			0.025				0.03
Medium cases	0.002	0.003	0.004	0.006		0.005		0.01		0.015		0.02		0.025			0.03				0.035
Very severe cases	0.002	0.004	0.006	0.008		0.01		0.015		0.02		0.025		0.03			0.035				0.04

This method has been used in Budapest since 1890. Simon reports 45,477 cases with 2 paralyses and 131 deaths. A markedly good effect from the Högyes method appears in the statistics from Welkevreden as quoted by Borger (Simon). Up to 1906 the intensive method of Pasteur was used with the following results:

1,379 Europeans treated with 10 cases of paralyses........1–138
2,073 Islanders treated with 1 case of paralysis...........1–2073

After 1906 Högyes' method was used with the following results:

751 Europeans treated with 1 case of paralysis...........1–751
2,189 Islanders treated with 0 case of paralysis

The advantages of this method seem to be its simplicity, its inexpensiveness, and, above all, its claimed good results.

Philips has recently reported a method for preparing a "standardized glycerinated rabies virus" from rabbit brains. For the first three days dead vaccine (killed by keeping at 37° C. for twenty-four hours) is given. After that living vaccine is used. The doses are regulated by dilution. This method has been in use at the Pasteur Institute of Columbus, Ohio, for five years. During this time 1,540 patients have been treated. The biting animal was proved rabid in all but 158 cases. Only 1 death occurred and that within fourteen days after completion of the treatment. We are now testing this method in our laboratory.

Superintensive Method.—The use of unmodified fixed virus in large doses has been given this name. It was advocated and practiced by Ferrán, of Barcelona, early in the history of the Pasteur treatment. In his original method Ferrán used comparatively large doses of emulsions of the fresh fixed virus brain. Ferrán states that he occasionally noted cases of rabies (as did others in the early days of antirabic treatment) which seemed to be due to the treatment itself. This he attributed to small particles of the virulent emulsion carried to the brain by the leukocytes. He then sought for a substance that would be positively chemotactic for the leukocytes and so hold them back. This he found in mercury, which in combining with the albumin in the virus forms an albuminate of mercury. Since using this modification he claims that he has excluded the harmful properties of the treatment without impairing the immunizing strength to any extent. It should be noted that Bareggi, using the original method of Ferrán in 1889, had 5 deaths from paralytic rabies due to fixed virus infection. The Italian government in consequence forbade the use of the early Ferrán method.

Fifteen thousand persons have been treated by the modified Ferrán method, with a mortality ranging from 0.2 to 0.4 per cent. Only one strength of emulsion is used for all patients, and the treatment lasts five days. All cases coming for treatment later than ten days after the bite are refused treatment.

Details of the Treatment.—Eighty c.gm. of virulent brains or cord are emulsified with 2 gm. of sterile sand gently and thoroughly in a mortar. Eight c.c. of fluid are added drop by drop. This fluid is a mercury preparation, which with the emulsion forms an albuminate of mercury. The mixture is allowed to stand one-half hour before decanting the fluid. This decanted fluid is used for the injections (6 c.c.) which are made each day in three injections on five consecutive days. In bad cases the course of treatment is repeated after an interval of from one to ten days. The treatment causes a moderate local induration sometimes lasting several months. If paralyses occur they are non-fatal.

Ferrán states that his inoculations should only be made subcutaneously, as cutaneous and intramuscular inoculations may produce infection. He claims that large amounts of the virus by the (hypothetical) toxin they contain produce an immunity more quickly than the living rabies germs, and so protect the patient from infection with the vaccine, while small doses of the vaccine might produce rabies.

In this country Proescher, of Pittsburgh, has used a similar method. He concludes that his strain of fixed virus (Pittsburg) is harmless for human beings because he injected two men each with an entire fixed virus brain intramuscularly without ill effect to them. A control rabbit injected subdurally with a 2 per cent dilution of the same died in seven days with experimental rabies. He further states that he has used doses fifty times as great as those of Ferrán, with no deaths from rabies infection. In 1911 he reports 92 cases which were treated by injections of unchanged fixed virus.

His technic is as follows: An amount of brain substance averaging from 0.10 to 0.12 gm. is removed by the jaws of a pair of urethral forceps. This is emulsified in 30 c.c. of salt solution. Three c.c. of this emulsion (equal to about 0.01 gm. of fixed virus) is injected subcutaneously. One injection is given each day for five days.

The most important result of the superintensive method is its demonstration of the harmlessness in the majority of people of large subcutaneous doses of fixed virus. However, until we know more of the conditions causing the susceptibility to fresh fixed virus infection which occurs in a small percentage of people, such large doses given at the beginning of treatment should be considered with reserve.

Serum-vaccine Treatment—*Roumanian Method.*—Babes began using antirabic serum as early as 1890. By combining it with the Pasteur method he found that it gave good results in severe bites such as those received from the wolf. He also tried combining the Pasteur method with heated virus. He has gone minutely into the subject of this treatment in his recent book, *Traité de la Rage.* He insists on individual alterations of treatment. As an example of his treatment of a very severe face wound see the schema below.

He simplified this elaborate method in 1906 (1) by beginning with a six-day cord; and (2) by giving only one series of heated cords in 10 c.c. doses. The treatment lasts from twenty to thirty days. With this modification he says that, while his absolute mortality from wolf bites remains at 5 to 6 per cent, not one case died after the fifteen-day limit of observation.

Babes' Treatment of Severe Face Wound

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Age of cord Dose=0.3–0.2 of a 1–10 emulsion	12 10 9 8 7 6	6 4 3 2 2 1	6 4 3 2 1	8 7	6 5	5 4	4 3	3 2	2 1	0	8 7	7 6	6 5	5 4	4 3	3 2	2 1	1	S*	0	S
Emulsion heated at 80° to 50° C. 20 gm. added to cord				80° 80°	75° 70°	70° 70°	65° 65°	60° 60°	55° 50°	0	80°	75°	70°	65°	60°	55°	50°				

* S means 20 gm. of antirabic serum.

After severe dog bites Babes does not use the heated vaccine, but does add the serum, according to the following schema. One dose is 3 c.c. of 1:10 solution.

Babes' Treatment After Severe Dog Bites

Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Cords	Light	6 5	5 4	4 3	3 2	6 0	0 0	6 5	5 4	4 3	3 2	2 1	0 0							
	Severe	6 5 5 4	4 3 3 2	2 1	1 0	6 5	4 3	2 1	0 0	0 0	6 5	5 4	4 3	3 2	0 0	2 1	0	20 gm. Ser.	0	20 gm. Ser.

Six thousand five hundred and twenty-five cases have been treated by this method, with 8 paralyses and a total mortality of 0.452.

Marie's Method.—For several years past the use of virus-serum mixture has been in vogue at the Pasteur Institute in Paris, the technic of which is as follows: 1 gm. of the medulla of a rabbit dead of fixed virus is finely emulsified with 9 c.c. of 0.8 per cent salt solution and filtered through linen. Two c.c. of this emulsion and 4 c.c. of antirabic serum (obtained from sheep, and inactivated at 56° C. for thirty minutes) are carefully mixed and allowed to stand for a time. Six c.c. of this mixture, which contains an excess of virus, is injected into the patient. These injections are repeated on the next three days, after which the treatment proceeds according to the regular Pasteur schema, beginning with the use of a six-day cord on the fifth day. The antirabic serum is obtained from sheep which have been subjected to a long and strong course of treatment with fixed virus. It is claimed that a quicker immunity is produced by the serum-virus mixture than by the original Pasteur scheme, an advantage of especial value in the treatment of cases liable to become infected with a short incubation, such as bites on the head. Three thousand nine hundred and ninety-three cases are reported treated by this method, with a mortality of 0.23 per cent.

Antirabic Serum.—The possibility that the serum of animals immunized against rabies contains protective substances was suggested by Pasteur as early as 1889. The following year Babes recommended the use of the serum of vaccinated animals in combination with the Pasteur treatment. Since then the study of the amount and character of the antibody content of animals immunized against rabies has been carried on more or less extensively both from the theoretic and the practical sides. It was hoped that a serum could be obtained that would effect a cure for developed rabies just as diphtheria antitoxin does for developed diphtheria. But such a definite applicability of the serum has not developed. It was soon found that, while serum of certain vaccinated animals possessed the property of neutralizing rabies virus in vitro, it had only a slight inhibiting power when inoculated into the living animal, and apparently no action at all by any method of inoculation after the disease had become manifest. Babes still claims, however, that the serum has enough effect in vivo to be used in treatment, and his serum treatment is based upon this claim. He gives as his reason for employing serum at the end of treatment that he wishes to introduce into the patient at the time he most needs it the largest amount of antibodies. He also claims that the serum so given will prevent or cure the occasional paralyses which occur during treatment.

Those who did not agree with Babes were led to test the practical use of the serum combined with the beginning vaccine inoculations.

Remlinger, Marie, and others showed that a serum-virus mixture with a slight excess of virus will protect an animal against infection into the anterior chamber of the eye when inoculated during the three days following the vaccination. Thus he showed that immunity is produced more quickly by these unsaturated mixtures of virus and serum than by the virus alone. If a surplus of serum is present the animals are not protected from a later infection. The results of Marie's method of inoculating dogs with only one injection of an unsaturated virus-serum mixture is shown by the following table:

Results of Marie's Method of Inoculating Dogs

Dog	Date of Injection	Amount Injected	Date of Infection	Result
1	Dec. 16	10 c.c.	Jan. 23	Living
2	Dec. 16	10 c.c.	Jan. 23	Living
3	Dec. 16	10 c.c.	Jan. 23	Living
4	Feb. 25	8 c.c.	Mar. 21	Rabies I-IV
5	Aug. 11	10 c.c.	Sept. 14	Living

A serum containing such properties is only found in animals that have undergone a protracted series of inoculations of gradually increasing strength. Marie, who has used the serum in humans since 1904, prepares it as follows: The brains of two rabbits dying from fixed virus infection are finely rubbed up with physiologic salt solution in the proportion of 20 gm. in 180 c.c. This emulsion is filtered through fine cloth and heated for one-half hour at 37° C. Sheep are used for the inoculation. Each sheep receives intravenously 30 c.c. (3 gm. fixed virus) a week for from six to eight weeks. Thirteen days after the last inoculation the first blood is drawn. Then in a period of two weeks, a total of 200 c.c. of blood are drawn at four bleedings. After a fourteen-day pause another series of inoculations is given and the animal is ready for another series of bleedings. From each animal yearly about 3 liters of antirabic serum are obtained.

Remlinger's method of inoculating sheep is to begin with three or four intravenous inoculations of fixed virus, and then to go on with subcutaneous inoculations until finally an entire fixed virus brain in 400 c.c. of normal salt solution has been inoculated.

The dose of the inoculated antigen is of importance in producing a high-grade serum. Smaller doses than those given above produce weaker serums, according to Tizzoni and Centanni, Marie and others. A strong serum is one that neutralizes 40 virus units in 1 c.c.

A *virus unit* is 1 c.c. of five times the dilution of fixed virus which will surely kill a rabbit inoculated intracerebrally; for example, the unit of a fixed virus that will surely kill a rabbit in 1:500 dilution is 1 c.c. of a 1:100 dilution.

ANTIBODY CONTENT OF THE SERUM (KRAUS)

Animals	Amount of Serum in c.c.	Amount of Virus in c.c.	Time of Making Inoculations after Mixture		Result
			Immediately	24 Hours	
Sheep	0.1	1.0 Dil. 1:100	+		Living
	0.05	1.0 Dil. 1:100	+		Living
	0.1	1:10 0.1 (not filtered) Dil.	+		Dead (rabies)
Dog I	0.05	1.0 Dil. 1:100		+	Living
	0.1 heated to 58° C.	1.0 Dil. 1:100		+	Living
Dog II	0.05	1.0 Dil. 1:100		+	Living
	0.05 heated to 60° C. for ½ hour	1.0 Dil. 1:100		+	Living
Horse	0.01	1.0 Dil. 1:100		+	Living
	0.01	1.0 Dil. 1:100	+		Living

The demonstration of antibody content of the serum may be shown by the above table of Kraus (Heller and Rothermundt in Kolle and Wassermann, 1913).

The nature of the antibodies in rabies serum has been the subject of many studies. Fermi and a few others claim that the antibodies are not specific. They say that they can obtain a similar serum after the inoculation of normal brain emulsions. Some even use normal brain emulsions in the treatment of their lighter cases.

Certain investigators (Kraus, Marie, and others), while not able to corroborate all of these claims, have found that the serum of certain animals which are more or less refractory to rabies possesses a small amount of rabicidal strength; for example, 0.5 c.c. of normal chicken serum mixed with one unit of fixed virus (1 c.c. of 1:100 dilution) causes the latter to become neutral in eighteen hours.

The neutralizing property is not due to a neurotoxic substance since animals stand very large doses of the serum without harm.

All species of animals tried produce the specific antibodies, but not to an equal degree. Human beings and monkeys are said to have more antibodies after vaccination than rabbits.

Statistics of Patients Treated at Pasteur Institute, Paris

Year	Persons Treated	Number of Deaths	Percentage	Year	Persons Treated	Number of Deaths	Percentage
1886....	2,671	25	0.94	1904.....	755	3	0.39
1887....	2,770	14	0.79	1905.....	721	3	0.41
1888....	1,622	9	0.55	1906.....	772	1	0.43
1889....	1,830	7	0.38	1907.....	786	3	0.38
1890....	1,540	5	0.32	1908.....	524	1	0.19
1891....	1,559	4	0.25	1909.....	467	1	0.21
1892....	1,790	4	0.22	1910.....	401	0	0.00
1893....	1,648	6	0.36	1911.....	341	1	0.29
1894....	1,387	7	0.50	1912.....	395	0	0.00
1895....	1,520	5	0.38	1913.....	330	0	0.00
1896....	1,308	4	0.30	1914.....	373	0	0.00
1897....	1,529	6	0.39	1915.....	654	1	0.15
1898....	1,465	3	0.20	1916.....	1,388	3	0.21
1899....	1,614	4	0.25	1917.....	1,543	4	0.26
1900....	1,420	4	0.28	1918.....	1,803	3	0.16
1901....	1,321	5	0.38	1919.....	1,813	3	0.16
1902....	1,005	2	0.18	1920.....	1,126	6	0.53
1903....	628	2	0.32	1921.....	998	1	0.10

Centanni showed that immediately after vaccination the animal is not fully protected, though its serum may contain antirabic qualities, while later the animal is immune, though its serum may not be able to neutralize the rabies virus. These facts point to a cellular immunity.

Results of Antirabic Treatment.—On the whole the results of protective inoculations against rabies are marked. In regard to the best method to use, we are still in doubt. The statistics from the older methods are about the same as those from the newer. Some of the newer methods have the advantage that the method of preparing the vaccine is simpler. The results obtained at the Pasteur Institute, Paris, from its foundation up to 1921 are given on page 132. This table gives only the corrected mortality.

Babes quotes the following total mortality for cases treated during a space of three years according to different schemes of vaccination:

Mortality for Cases Treated According to Different Schemes of Vaccination

Locality and Method	Cases Treated	Mortality Per Cent
Bucharest (Roumanian method)	3,091	0.12
Paris (Pasteur method)	2,115	0.61
Berlin (modified Pasteur method)	934	1.28
Vienna (Pasteur method)	762	1.04
Budapest (Högyes method)	8,658	0.77

But these figures tell us little about the actual value of the different methods. In order to be able better to judge, the statistics should uniformly give many more details. Some institutes give such details, others do not. Until some such scheme as the following is carried out by all, we must change cautiously a treatment that has already given good results.

Points to be noted concerning cases treated with rabies vaccine are:

1. Diagnosis of biting animal:
   (*a*) Rabies, (*b*) probably rabies, (*c*) questionable, (*d*) not rabies, (*e*) nothing known.
2. Manner of making diagnosis:
   (*a*) By animal inoculation, (*b*) by microscopic examination, (*c*) by clinical diagnosis.
3. Site and character of bites (for example, number, depth, laceration, protected by clothing, etc.):
   (*a*) Head, (*b*) hands, (*c*) other parts of body, (*d*) contact with saliva but not bitten.
4. Time elapsing between bite and beginning of treatment.
5. Method of treatment used.
6. Complications during or after treatment, particularly paralysis.
7. Character and time of death.

That the time after the bite makes a great difference is shown by the table on page 134.

Immunity.—The immunity in human beings produced by the antirabic treatment apparently lasts a variable time. That it may not last more than fourteen months is shown by the history of one of our cases.

DIFFERENCE CAUSED BY ELAPSE OF TIME AFTER THE BITE

Time Intervening between Bite and Beginning Treatment		Number of Cases Treated	Death	Percentages
Babes	1 to 2 days	3,406	3	0.088
	3 to 5 days	2,541	2	0.077
	5 to 6 days	809	1	0.124
Diatroptoff	1 week	4,602	26	0.560
	2 weeks	961	16	1,660
	3 weeks	313	10	3.190

The patient was an assistant in a hospital for dogs. He was given eighteen days' treatment after a light wound on the hand from a rabid dog.

Fourteen months later he came down with typical hydrophobia. Since his treatment he had become very careless with cases of rabies, exposing wounded hands to saliva because he considered himself immune.

He was warned that there might be danger. Six weeks before his death he put a wounded hand into the mouth of a rabid animal.

There is little doubt but that this is a case of reinfection after loss of protection from the treatment rather than one of delayed hydrophobia.

Marie has found complete immunity in dogs eighteen months after treatment.

Contra-indications for Treatment.—No obvious contra-indications exist. That extremely few people have an individual susceptibility from unknown causes is probable. The results of this condition are taken up in the next section.

Ill Effects of Treatment—*Local.*—There is only slight local discomfort, increased a little if the emulsion contains glycerin. During the second week an erythema often appears about the point of inoculation, which Stimson regards as a manifestation of hypersusceptibility to foreign nerve tissue. It disappears in a few days. Geiger has given a good description of local reactions of the Pasteur treatment.

Constitutional.—Ever since the beginning of treatment occasional non-fatal affections of the nervous system have been reported, which occurred during or shortly after the course of treatment. These have varied in degree all the way from a slight neuritis, through paraplegias to paralysis of various parts of the body. Very occasionally the paralyses are marked and the patient dies. Cases of true paralytic rabies which may occur within the period required for the establishment of immunity by the treatment must be differentiated from cases occurring as a result of treatment.

Remlinger, in 1905, collected the cases of this character so far published. Poor, in 1908, published the few occurring among the many treated by the New York City Health Department. Fielder's table of our results is given under Modifications of Treatment. We have had no case of paralysis since 1914 in the 3,000 or more patients treated during that time.

The following table which Simon gives we copy in order to show the small percentage of these cases that have occurred during the whole time the treatment had been used in the places named up to 1912:

Cases Occurring during Time of Treatment up to 1912 (Simon)

Name of Institute	Number of Cases		Name of Institute	Number of Cases	
	Paralyses	Treated		Paralyses	Treated
Berlin	4	4,221	Kasan	2	2,407
Breslau	2	985	Wilna	3	8,522
Paris	6	32,045	Charkow	8	24,051
Algiers	2	4,755	St. Petersburg	1	13,000
Milan	6	2,942	Athens	4	6,588
Bologna	6	3,062	Constantinople	1	3,291
Naples	2	4,578	Weltewerden	12	6,392
Fraënza	1	1,440	Florence	1	3,262
Turin	2	2,207	Madrid	0	3,000
Palermo	4	7,129	Total	100	211,774
Barcelona	3	1,784	Odessa	1	....
Lisbon	1	12,888	Minnesota	2	....
Budapest	2	49,382			
Krakau	2	1,424	Total	103	....
Bucharest	15	7,056			
Jassy	10	5,458			

Only 1 paralysis occurred in 2,117 cases, or 0.048 per cent. As less than one-fourth of these have been fatal, including those cases known to have resulted from fixed virus infection, the total mortality is less than 1 in 10,000.

This table does not include the 7 cases from the New York City Health Department or the 3 reported from the Hygienic Laboratory at Washington. A number of these cases have occurred in those receiving the treatment, but not bitten by rabid animals.

Simon classifies the cases collected by him according to the diagnosis of the biting animal, with the mortality in each group as follows:

Cases Classified According to Diagnosis of Biting Animal

Positive Group		Probable Group		Questionable Group		Negative Group		Not Known Group	
Number Cases	Per Cent	Number Cases	Per Cent	Number Cases	Per Cent	Number Cases	Per Cent	Number Cases	Per Cent
25 (2†)*	29.76	11 (4†)	13.0	21 (5†)	25	17 (3†)	20.23	10 (5†)	11.9

* † Death.

Nineteen deaths occurred, as seen from the figures in parentheses, or 22 per cent of the 84 cases.

In analyzing the effect of different methods of treatment on paralyses, Simon gives the following summary:

EFFECT ON PARALYSES OF DIFFERENT METHODS OF TREATMENT

Method	Number of Cases Treated	Cases of Paralyses	Proportion
Classical Pasteur method	32,676	6	1:5446
Modified Pasteur method	8,657	16	1:541
Högyes method	51,417	3	1:17139

It is seen that the number of paralyses following the Högyes method is markedly less than that following the other methods.

From the studies so far made of these paralyses, the possibility of there being different causes for different cases cannot yet be ruled out. The chief theories advanced as to factors in producing the condition are six:

1. Due to "laboratory rabies" from the fixed virus vaccine inoculated.
2. Due to "modified rabies" resulting from the treatment on the street virus infection.
3. Due to a toxin produced by the rabies organisms.
4. Due to infection with extraneous organisms introduced with the virus during treatment.
5. Due to psychologic disorders.
6. Due to the inoculation of a foreign proteid with a subsequent anaphylactic reaction.

Simon includes Bereggi's 5 cases of undoubted fixed virus infection. These were cases that had been inoculated with large doses of unmodified fixed virus, and test-animal inoculations showed fixed virus infection. These cases must have had a special predisposition or the virus must have been especially virulent, since many cases in different parts of the world have been inoculated with large amounts of unmodified fixed virus and have shown no symptoms.

One of the other fatal cases (following the Berlin intensive method) that was tested showed fixed virus in his brain, and one showed street virus infection. Hence the first and second theories cannot yet be ruled out as factors in at least a few of the cases. Five of the cases tested showed no rabies virus in their brains, therefore the third or the sixth theory may be applicable to them. Unfortunately 7 of the cases were not tested. The fourth and the fifth theories may also be ruled out, since, if ever applicable, they would be so only in very infrequent, unimportant, non-fatal cases, as is shown in some of those that Poor reported.

We may conclude that the third and the sixth theories embrace the two most probable factors in the majority of the cases of paralysis.

Treatment of the developed disease is simply palliative and non-specific.

Summary of Present State of Specific Treatment of Hydrophobia.—1. The specific vaccine treatment by attenuated virus or by dilutions of fresh virus protects the great majority of the cases that begin treatment immediately after the infection; the very few unprotected ones are among those who have been bitten very severely or who have been infected with an unusually virulent virus or who are peculiarly susceptible.

2. Antirabic serum alone possesses neither a protective nor a curative action; combined with the vaccine so that the latter is not completely saturated, the mixture seems to produce a quicker and stronger immunity.

3. The comparative worth of the many methods advocated for the preventive treatment of rabies cannot be positively determined until standard rules for the recording of statistics are adopted.

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CHAPTER VI

MUMPS

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REVISED BY GROVER F. POWERS

Synonyms.—Latin, cynanche parotidæa. parotitis epidemica; French, les oreillons; German, Ziegenpeter; Spanish, murria; Italian, stranguglioni.

Definition.—This is a specific infectious disease characterized by fever, a certain amount of disturbance of the general system, and a swelling of one or more of the salivary glands. As a rule, the swelling is confined to one or both of the parotids. Sometimes the submaxillary or sublingual glands may be involved, together with the parotid, and at other times one or all of these last-named glands may be the only manifestation of the disease. In some instances the pancreas is involved, usually as a complication; but in some cases the disturbance in the pancreas is the only change which may be noted. Diagnosis in these cases, of course, could not be made apart from an epidemic of mumps.

Complications.—The most frequent of these is the swelling of the testicle and epididymis in the male, and, of less frequence, swelling of the labia majora or of the ovaries in the female. In addition to these there is not infrequent involvement of the mammary gland either in males or females. A complication of less frequent occurrence is the extension of the disease, or, at any rate, of the swelling, to the tonsil, pharynx and larynx (edema), to the conjunctiva and tissues above the eye, and to the subcutaneous tissues below the parotid—the swelling in some instances reaching remarkable degrees. Of still less frequent occurrence are the inflammations occurring in the lacrimal glands, in the thyroid, sometimes in the thymus, and pancreas; and of particular importance is the involvement of various parts of the ear, of the eye, and of the nervous system—chiefly in the form of a polyneuritis or meningitis. Cytochemical changes in the spinal fluid are present in most, if not all, patients with mumps, whether or not frank signs of meningeal irritation are present.

History.—The disease has been known from the earliest times. Hippocrates has given a most interesting description; and he noted an epidemic occurring in Thasos. He also observed the frequent involvement of the testicle. Since his time the disease has been referred to by various writers, including Galen, Celsus, and Aetius. Its contagiousness was referred to by Mangor in 1773, and Hirsch, in his *Handbuch der historische und geographische Pathologie,* has given a list of the epidemics of the disease, the first one of which, in America, was described by Chalmers from Charleston, South Carolina, in 1744, and the second one, in the same locality, was described by the same author in 1768.

The disease is more frequent in winter than in summer, and, while it may occur at any age, it is most frequent between the ages of five and fifteen years. A curious feature of the disease is the fact that *it may recur;* and Catrin has observed this in 6 per cent of his cases, which is certainly higher than in the experience of most authors. Gerhardt has noted an instance in which the recurrence took place in nineteen days after the original disease had subsided. The course of the recurrence is quite similar to the original attack. It should also be noted that mumps may occur with other diseases.

Mumps is a disease in which comparatively few pathological and bacteriological studies have been made. A number of organisms have been described. One of the most complete studies is that by Laveran and Catrin. They obtained an organism in pure culture from the parotid gland (by puncture), also from the testicle, the edematous tissue, and the blood. The organism was a micrococcus occurring in pairs, which grew on ordinary media, and was easily stained with ordinary dyes and decolorized by Gram's method of staining. These results have been confirmed by Darling and others, but perhaps not sufficiently. Merelli, of Pisa, claims to isolate an organism, which he calls Micrococcus tragenus, from the blood and from the serous fluid in the testicle from cases which were complicated with orchitis. It does not stain with Gram's method. Inoculations on small animals in the laboratory were negative, but the organism gave the agglutination tests in dilutions as high as 1 to 500. Rosenow studied an epidemic of parotitis and appendicitis, and found a coccus which produced lesions of the parotid in rabbits and dogs. The organism resembled that described by Herb. As a result of experimental work, particularly that of Gordon and Wollstein, it is pretty generally agreed that mumps is caused by a filterable virus.

Susceptibility.—It is interesting to note that, while the majority of cases occur between the ages of five and fifteen, after fifteen years the susceptibility apparently diminishes with age, although individuals of sixty or seventy are not entirely immune. Under five years the susceptibility to the disease is not great, and nursing infants, as a rule, are immune, and may even nurse the breast of a woman with mumps without taking the disease. Instances of the disease occurring in nurslings, however, have been reported. White has reported a case of a woman whose child showed signs of the disease six days after delivery, and the woman herself had a swelling of the parotid on the following day. Comby cites a case in which a woman, eight months pregnant, developed mumps, and her child, born at term, showed marked swelling of the parotids and had difficulty in swallowing, which increased for two days, when the swelling gradually disappeared. The incidence of the disease is particularly high among army recruits from isolated or rural districts.

Transmission and Infectiousness.—The disease is one which is apparently contracted by direct contact; and almost all of the cases occur in this way. The disease is evidently transmissible before the symptoms appear. The infectiousness is probably most marked in the beginning of the disease, and may persist, certainly in some instances, as long as six weeks after the disappearance of the symptoms; although usually a patient may be considered safe to associate with others three weeks after the symptoms have disappeared; and doubtless a great many before this period has elapsed. As we have no means at the present time of telling whether a person is capable of transmitting the disease or not, three or four weeks should be allowed to elapse before the individual is permitted to go about, especially if there is any wish to avoid infection of others, as there always should be. In the case of children this is usually easy to secure, but in adults otherwise actively occupied in important affairs such a long period of isolation is scarcely practicable. The disease is not transmitted through the air to any great extent, and, while it is possible for an otherwise healthy person to carry the disease without contracting it himself, this is certainly a very exceptional occurrence. In these instances the virus is apparently carried in the mouth of healthy individuals closely associated with mumps, and may be transmitted by kissing. *Transmission by fomites* is certainly very rare, and almost unknown, although Roth relates a case in which the disease was contracted by sleeping in a bed previously occupied by a patient with mumps. In a disease like mumps it is so difficult to exclude the possibility of infection by direct contact with individuals having, or about to have, or who have recently had, the disease, that evidence as to its transmission by means other than direct contact must be regarded with considerable suspicion. Epidemics in institutions are not infrequent. They may occur in schools, and not infrequently in barracks. The number of people affected varies in different epidemics, and according to the age of the individuals exposed. Usually from one-fourth to one-third of those coming in contact with the disease will take it. *Epidemics in institutions* are usually slow and last several months, new cases developing from time to time; and they are often curiously confined to one part of a building or to one enclosure.

Incubation.—The incubation period is usually long and is variously stated by different observers. The average is from seventeen to twenty-one days. Variations are placed at from three to twenty-five days or longer. The Commission of the Clinical Society of London placed the limit from fourteen to twenty-five days. There have been undoubted cases, however, where the disease developed after thirty-five days (Parker Douglas), and even after six weeks (Bernutz). The incubation period in experimental animals is shorter than in human beings. One attack usually confers immunity. While recurrences are not uncommon, second attacks are more or less rare, but they may occur at times, and even third attacks have been reported.

Prophylaxis.—The prophylactic treatment consists in isolation. This is of especial importance in cases of young soldiers and school children. For practical purposes four weeks after the onset of the disease the patient may be allowed to mingle with others. This is an arbitrary rule, but one which certainly will give satisfactory results in most instances. Longer periods of isolation are not advisable on account of the great loss of time; and very few infections take place after this period has expired. It must be remembered that epidemics are often set up or continued by individuals who have been exposed to the disease and who infect others just before the symptoms are manifest, or just after they have begun. Under ordinary conditions these individuals who have been exposed to the disease are disregarded, because it involves a great loss of time, as three or four weeks would have to elapse before the individual could be reasonably sure not to be a source of danger. In schools with medical supervision, if the children are allowed to go to school, they should be under the most careful observation between the second and third week after they have been exposed to the disease. Children who have had the disease previously, and who are living in the house with cases of mumps, may be allowed to attend school. The use of some antiseptic mouth wash in these cases would certainly not be amiss. In the case of barracks all the individuals exposed should, as far as possible, be confined to the same building or group of buildings, and not allowed to mingle with others under ordinary circumstances until the period of incubation is over.

Hess has suggested a method of protecting patients from mumps. He used from 6 to 8 c.c. of blood drawn from a donor and injected intramuscularly. This blood was taken from three groups of children: some from a patient who had just recovered and in whom there was some swelling of the parotid, some from patients recovered about ten days, and some from those who had had the disease several years previous. There were no local or constitutional reactions and none of twenty children so treated contracted mumps, although exposed to it.

Treatment.—The treatment of the disease itself is rather simple, although there are complications, at times requiring more or less attention, and this is of especial importance in the case of young males, as it undoubtedly reduces the tendency to a metastasis in the testicle. *Rest in bed for eight or nine days is the only form of treatment upon which* *reliance can be placed.* The *food* should be liquid, if there is much difficulty in taking it; although any soft or easily swallowed food may be allowed. In some instances the difficulty of opening the mouth is so great that the food must be taken through a tube or a straw. Milk, custards, and egg-nog are the most suitable for this purpose.

It is usually well to give the patient a purge at the outset, some simple saline, sulphate of soda, or phosphate of soda, or magnesium sulphate usually being preferred. If the *temperature* is high, the patient is nervous and uncomfortable in consequence, and the use of ice-bags to the head or sponging with tepid or cool water or equal parts of alcohol and water may be resorted to. It is scarcely advisable to administer antipyretics to reduce the fever; although, if the nervous symptoms are marked, as they sometimes are, the administration of antipyretics with or without bromids or codein sulphate may be considered. *Pain* is a very variable symptom, some patients not suffering at all, while others are exceedingly uncomfortable. I believe that antipyrin and codein sulphate in combination will give greater relief from the pain with less general disturbance than any other anodyne that may be used, although there is no objection to the administration of some forms of opium, should the physician prefer it. The after-effects are more marked, however, both in the general discomfort and liability to headache, as well as constipation. The pain may often be controlled by local applications, and various methods have been advised. In some the use of the hot-water bag or an electric heater gives great relief, while others prefer the application of cold in the form of an ice-bag. Whether one chooses heat or cold depends upon the personal equation of the patient. All things considered, I believe the cold gives more relief in a greater number of cases than heat, and certainly tends to reduce the fever at the same time. The patient who complains of discomfort from the ice-bag when it is first put on will frequently ask for it if its use is persisted in long enough for him to get accustomed to it. Of the *local applications* to the gland, 5 per cent guaiacol is frequently used either with glycerin or rubbed up with an ointment. Belladonna ointment has been found to be effectual in relieving pain, and many physicians use methyl salicylate painted over the gland two or three times a day. Other local applications need hardly be mentioned, although all sorts of things have been advised. In some instances the *swelling of the gland persists.* In these cases *gentle massage* may be advised, using cocoa butter as a lubricant, and having massage done for five or ten minutes twice a day. The use of iodid of potash ointment has been suggested in these cases, but the internal administration of iodid of potassium in 5 or 10-gr. doses three times daily, and in some instances even larger amounts than this, will be found to be more effectual. Where there is marked *anemia,* together with the chronic swelling, the internal administration of the syrup of the iodid of iron is to be advised. *Mouth* *washes* are usually useful, although sometimes difficult of application. The cleansing of the teeth may be impossible if there is much swelling. Equal parts of peroxid of hydrogen and water, saturated solution of boric acid, and 1 per cent permanganate of potash are usually recommended. Dobell's solution or Seiler's solution may be used. Eustace Smith suggests a saturated solution of salol in an ounce of alcohol, to which 40 drops of chloroform have been added. Thirty or 40 drops of this solution in a tumbler of warm water will be found to be a pleasant antiseptic wash. In some instances there is *excessive ptyalism,* and this may sometimes be relieved by full doses of atropin. In other cases there is stenosis of the duct, which leads to a dry mouth; Burton has suggested the insertion of a probe into the duct and the use of a constant current in these cases. Sometimes, even when the duct is not stopped up, there is a lack of secretion which leads to a most unpleasant *dryness of the mucous membranes* of the mouth. This may be alleviated to a certain extent by mouth washes containing small amounts of glycerin. In some instances the patients suffer from a lack of fluid, the blood actually getting thicker, as in Asiatic cholera. This may be relieved either by rectal injections of normal salt solution or plain water, or, if that should be contra-indicated for any reason, by subcutaneous infusions of salt solution. Where there is *excessive swelling of the uvula or mucous membranes of the throat,* it is sometimes necessary to scarify these tissues with a sharp knife, all except the point, which should be carefully guarded by the use of a bandage. There have been instances in which *edema of the glottis* developed. Where this occurs, tracheotomy promptly done is the only thing which is of any avail. Meningitis should be treated by general measures devised for this disease, and lumbar puncture should be done to relieve pressure.

The question of *suppuration* in mumps is one of considerable importance. The redness and semifluctuation which may be present frequently suggest an abscess when none is present. Inasmuch as suppuration in mumps is exceedingly rare, and frequently suspected where it does not exist, a very good rule is not to incise the gland unless the diagnosis is quite certain. Should suppuration occur, or be suspected, it is a good plan to use a very small-bladed knife, and make a very small incision until the pus is located, when it may be made sufficiently large. Care should be taken not to cut the branches of the facial nerve; consequently the cut should be made in lines radiating from the exit of the facial nerve, and should be kept back of the line drawn from the zygomatic arch to the angle of the jaw.

The treatment of *orchitis* and *epididymitis* is very important. There is atrophy of the testicle in perhaps two-thirds of the cases regardless of the treatment instituted, yet it is quite probable that rest and the proper protection of the gland may have something to do with its conservation.

The treatment consists in rest in bed and the proper support for the inflamed gland, which can usually be secured by cushions or cotton. Application of cold is one of the most satisfactory means of controlling pain. Many local applications have been suggested, chief of which are belladonna ointment and guaiacol, as suggested above. Martin has suggested the injection of 0.01 gm. of pilocarpin. This may be repeated every second day. He states that it shortens the course of the inflammation and relieves pain. It is well to bear in mind that the usual course of the disease is from six to nine days, although in some instances it may be prolonged to two weeks or occasionally even longer. If the pain is very severe, anodynes of various kinds may be administered internally. The use of galvanic or faradic electricity has been suggested to prevent atrophy, but the success with which this is attended has never been very satisfactorily demonstrated. George G. Smith has suggested treatment of the orchitis by means of operation, which consists of a two-inch vertical incision along the anterior aspect of the left side of the scrotum and then the opening of the tunica vaginalis. The fluid is allowed to escape after the tunica is opened over the epididymis in several places. A rubber drain is used and the scrotum tightly compressed in an Alexander bandage. The drain in a case that was operated on was removed three days later. Too few cases have been reported on to speak definitely about this form of treatment. Injection of diphtheria antitoxin and of electrargol followed by aspirin have been reported as successful curative measures in orchitis. The treatment of the involvement of other glands, such as the lacrimal gland, the thyroid, or the thymus, is best carried out by local applications of cold. Nephritis and the other complications are treated on general therapeutic principles. The meningitis of mumps requires no special treatment.[1]

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[1] The pancreatitis of mumps occasionally requires laparotomy and pancreatic drainage, as in the case reported by Louise Farnam.—Editor.

CHAPTER VII

FOOT AND MOUTH DISEASE

Allan Ramsey

Revised by George Blumer

This is an acute infectious disease of animals which is occasionally transmitted to man. It is due to a filterable ultramicroscopic virus discovered by Löffler and Frosch in 1898. It is both directly and indirectly contagious for human beings. Among the lower animals the disease prevails in epidemic form, the extent and ravages of some of the epidemics being tremendous. It occurs frequently and extensively in the European countries, but in this country it is rare. In Germany, in 1892, there were 4,153,539 domestic animals affected; the following year there were 500,342.

In man foot and mouth disease usually occurs sporadically, but occasionally it appears as an epidemic. Considering that the disease is communicable to man, and that the epidemics among animals are so extensive, it is astonishing that the disease is so rare in human beings. When it affects human beings it generally attacks children and is due to drinking milk from infected animals.

While the specific cause of the disease has not as yet been seen, the infectious material exists in the liquid contents of the vesicles, in the secretions from the ulcers, in the milk tainted by the vesicles and ulcers, and possibly in the urine and feces.

The lymph from the vesicles, when inoculated into calves, promptly produces the disease. Nevertheless, no bacteria can be found in this lymph either by the microscope or by cultural methods. The lymph can be filtered through the finest porcelain filter, and it still retains its virulence. The virus must, therefore, belong to the ultramicroscopic, and in this respect is similar to that of such diseases as small-pox, scarlet fever, and measles. It is the most infectious and virulent toxin or virus known among animals.

Prophylaxis.—Prevention of this disease is of the first importance and the prophylaxis of the disease in man is naturally closely connected with that of the disease in animals. At the present time prophylaxis among the domestic animals means chiefly the limiting and stamping out of the disease after it has made its appearance. There is no successful method of direct treatment of the disease itself. Vaccination has been tried, but up to the present time no satisfactory vaccine has been devised.

The following illustrates much that is of interest in both the subjects of prevention and transmission. In November, 1908, an outbreak of foot and mouth disease was discovered among some Pennsylvania cattle. A prompt investigation of the epidemic by the federal government disclosed the fact that some of the small-pox vaccine virus, imported from a foreign country, was contaminated with the disease. When this vaccine was employed for the production of vaccine in calves, the calves became infected with the foot and mouth disease. This occurred with only one concern manufacturing biologic products; from this concern another purchased the contaminated vaccine and infected its own calves. The calves of the second firm, which were now infected with the foot and mouth disease, were finally sold in the open market and they started the epidemic. The calves of the first firm, after they had served their purpose for the production of small-pox vaccine, were killed by the firm in accordance with its usual custom of dealing with its own animals.

The government immediately withdrew the license of both these firms, all their small-pox vaccine was at once recalled from the open market, and by this and other vigorous measures the epidemic was promptly checked and eradicated. This one episode cost the federal government $300,000.

No instance of foot and mouth disease communicated to man through small-pox vaccine has been recorded.

The disease in cattle is to be dealt with by means of slaughter of infected and exposed animals, by quarantine and by disinfection of stables and premises involved. Slaughter, combined with quarantine and disinfection, is the method in the United States; in Germany, where the disease is endemic, this method is too costly and would destroy too large a part of all her animals. In our country the federal government pays one-half and the state government the other half of the value of the animals destroyed. In this country in 1914 we had our most severe and most extensive epidemic, which was handled by these methods.

Prophylaxis in man involves the following measures: First, the patient should be isolated. Among a dairy or peasant population this is not easy. Persons with cuts or erosions upon their hands should abstain from milking diseased cows. Secondly, the milk from infected cows should be boiled as such milk is capable of producing the disease. During epidemics it would probably be best to boil all milk and thus reduce the danger to the minimum. Meat from infected animals should be boiled; butter, cream and cheese from such sources should not be used at all.

Treatment.—The general treatment is dietetic and symptomatic, and requires no description. Attempts at a prophylactic serum are not yet successful, although Löffler and Frosch have done much valuable work in this direction.

The chief treatment is directed to the care of the inflammatory condition about the lips and mouth; efforts should be made to give relief from the pain and to prevent secondary infection of the ulcers. This is accomplished by touching each ulcer with nitrate of silver. Baginsky advises the use of a ⅓ per cent solution of permanganate of potash. A 2 per cent solution of chlorate of potash may be employed as a gargle.

Fatalities are rare, and when they do occur they are found most frequently among children.

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INFECTIOUS DISEASES OF UNCERTAIN OR UNKNOWN ETIOLOGY

CHAPTER VIII

MEASLES

Francis G. Blake

Although measles itself is a comparatively mild, self-limited disease, its prevention and treatment are nevertheless of the greatest importance because of the severe and not infrequently fatal complications to which it leads. Many factors are concerned in the incidence of complications. Age and previous state of health both play a significant rôle. Of equal or even greater importance are the environmental conditions under which patients with measles are treated, especially with respect to opportunities for exposure to sources of secondary infection.

The relation of age and previous state of health to mortality in measles is generally recognized. Other things being equal, measles is much more dangerous in infancy and early childhood than later in life. From the sixth month until the end of the second year the mortality is about 20 per cent, during the third year about 15 per cent, while after this time it rapidly diminishes until it becomes very low in adult life under ordinary circumstances. That measles may constitute a grave menace to life even among adults is thoroughly established. When outbreaks occur in army recruit camps, in prisons and other institutions, the death-rate may become very high. In this connection it is important to emphasize that it is not age but the group treatment of large numbers of individuals with measles which is the determining factor in the high mortality. Under these conditions serious complications due to secondary infection become frequent and often assume epidemic proportions.

The influence of preëxisting disease such as congenital syphilis, tuberculosis, rickets, and other malnutritional states in increasing the case fatality rate of measles is well known and requires no comment.

The relation of the conditions under which patients are treated to the incidence of complications and consequently to mortality, since the one determines the other, is likewise well established but not so generally appreciated. Failure to protect the individual with measles against secondary infection from exogenous sources inevitably results in an increased incidence of complications. This is most strikingly exemplified when patients are treated under crowded conditions whether in hospital wards or in the homes of the poor. Even under the best conditions the danger is present unless precautions are taken to prevent the transfer of pathogenic organisms to those sick with measles.

From the foregoing general considerations it follows that the most important principle in the prophylaxis of measles is the postponement of the occurrence of measles as long as possible or at least until the dangerous age period is past; that the most important principle in the treatment of measles is the prevention of those conditions which lead to the development of complications.

Prophylaxis.—Because of the widespread belief among the laity that measles is a disease of little importance which is inevitably contracted sooner or later and the sooner the better, the position is sometimes adopted that it is not worth while to prevent it. The extreme contagiousness of measles, the universal susceptibility to it, and the continued failure to control effectively its spread from individual to individual are too often advanced as arguments in support of this point of view. That this attitude is not justifiable should need little argument. It is the duty of the physician to use every means at his command to prevent disease not only as a measure of public health but in the individual as well. Even though it is undeniably true that the measures which we possess for the prevention of measles are far from satisfactory and often ineffective, this fact is no justification for permitting unnecessary exposure to measles or failing to utilize every measure that is available in an effort to prevent or at least to postpone the occurrence of the disease until the age period when complications are less frequent.

Many factors contribute to make the prevention of measles a most difficult problem. Lack of precise knowledge of the cause of the disease, its extreme contagiousness in the prodromal period, often before the diagnosis can be made with certainty, and the almost universal susceptibility to it are the most important. In spite of these serious handicaps, clinical observation and experimental investigation have at least provided a rational basis for the measures employed at the present time and, while these leave a great deal to be desired, nevertheless much can be accomplished in checking the spread of the disease by the application of the best methods available in our present state of knowledge. These methods are: (1) immediate isolation of actual and suspected cases; (2) quarantine of exposed susceptibles; (3) prophylactic inoculation of exposed susceptibles with convalescent measles serum.

Isolation and Quarantine.—The successful application of isolation and quarantine measures to the prevention of any transmissible infectious disease demands a precise knowledge of the sources of infection and the means of transmission of the infectious agent. This knowledge becomes of practical value when there can be developed from it methods for controlling and eliminating the sources of infection and for preventing the transfer of infection from person to person.

In the case of measles the sources of infection have been established with reasonable certainty by means of clinical observation supported by experimental investigation on the transmission of measles to monkeys. Briefly, the only known source of infection is a patient with measles. This fact greatly simplifies the problem of prophylaxis since other sources of infection such as food, water, milk, fomites, chronic carriers of the virus, insect vectors, etc., may be eliminated from consideration. On the other hand, the fact that measles is highly contagious during the early stages of the disease renders the problem most difficult, since the source of infection frequently goes unrecognized until after the transmission of the disease has already occurred.

As a guide to rational isolation and quarantine measures the following data are applicable:

Measles Not Transmissible During the Period of Incubation.—While the foregoing statement has not been conclusively proved by experiment, it is, nevertheless, generally accepted as true on the basis of clinical observation. At least there is no evidence in support of the view that measles follows exposure of susceptibles to those in the incubation period of the disease. Practically, a difficulty may present itself in rare instances, namely, to determine when the period of incubation ends and the period of invasion begins. In healthy and normal children the period of incubation of measles is not accompanied by any disturbance of health. Under these conditions a mistake as to the time of onset of the disease will rarely be possible. Three exceptions may be made. In the presence of preëxisting disease, especially if the disease is accompanied by inflammation of the upper respiratory tract, the determination of the beginning of measles may be very difficult or almost impossible. The second and more frequent exception is the failure to suspect the presence of measles, particularly in the absence of known exposure or at a time when measles is not prevalent in the community. Thirdly, in mild cases the symptoms of the period of invasion may be so slight as to escape notice and the presence of measles is not suspected until the exanthem appears.

Measles Contagious During the Prodromal Period (Period of Invasion, Catarrhal Stage).—The present view, which has been established positively by clinical observation and animal experiment, is that the disease is highly contagious during the prodromal period before the appearance of the skin eruption. While there may be some difference of opinion as to whether the period of greatest contagion is during the prodromal period or at the height of the eruption, the fact remains that the period of invasion, in one sense at least, is the most contagious, since the greatest number of cases follow exposure to measles in this stage of the disease. Unless this is understood and accepted, it is almost futile to attempt to prevent the spread of the disease. Fortunately, a group of characteristic symptoms exist during this period which make early recognition of measles possible. Koplik's spots, the respiratory and ocular symptoms, and fever with absence of leukocytosis, often a leukopenia, are the important signs. In the majority of instances these characteristic features are sufficiently pronounced to warrant a diagnosis; certainly sufficiently positive to warrant immediate isolation until there is no doubt as to whether the disease is measles or not. In exceptional instances the diagnosis cannot be made and no suspicion that the disease is measles arises during the period of invasion, either because the period of invasion is very short, or the symptoms are very slight and not characteristic.

Measles Contagious During the Stage of Eruption.—It has generally been accepted on the basis of clinical observation that measles is contagious during the early days of the exanthem. This opinion is supported by the experimental observations of Anderson and Goldberger, Blake and Trask, etc. These authors have shown by animal inoculation experiments that the virus of measles is present in the secretion of the upper respiratory tract up to forty-eight hours after the appearance of the exanthem. How much longer the period of contagion may last is not known with absolute certainty. Seigert claims that after the third or fourth day of the eruption no contagion exists. This would appear to be supported by the observations of Anderson and Goldberger and Blake and Trask who found that the nasal and buccal secretions collected later than seventy-two hours after the beginning of the eruption fail to cause measles in monkeys. While these results cannot be held to be conclusive for man, since the susceptibility of the monkey is probably not so great as that of man, they are at least very suggestive. Seven days after the appearance of the exanthem, providing the eruption has faded and the individual is otherwise well, is with little doubt a safe limit.

Measles Not Contagious During the Period of Desquamation and Convalescence.—This statement is generally accepted at present although there is no conclusive proof apart from clinical observation. The experiments of Anderson and Goldberger, though too limited in scope to be considered conclusive evidence, nevertheless confirm this view.

Mode of Transmission Directly from Person to Person.—Since it has been seen in the preceding paragraphs that the only known source of infection in measles is measles from the beginning of the period of invasion until the fading of the exanthem, it follows that the mode of transmission is from man to man either directly or indirectly. Nearly all authors are agreed that direct transmission is the rule and that transmission by fomites or by a third person is very unusual if it occurs at all. Close proximity is undoubtedly required but actual contact is not necessary. Since it has been demonstrated that the virus is abundantly present in the secretion of the respiratory tract it seems reasonable to assume that the infection is ordinarily conveyed by the droplets disseminated from the nose and mouth during coughing and sneezing. Whether the virus is conveyed by other means is not known. Holt believes that transmission by a third person but rarely happens and then only when the contact between the sick and well is very close and when the interval between is very short. If the contention of Seigert is correct, that the virus of measles does not retain viability for longer than two hours outside of the body, the rarity of indirect and the frequency of direct contagion will be satisfactorily explained. Final knowledge on these points must await the discovery of a method for isolating and identifying the cause of measles.

On the basis of the foregoing observations it is comparatively easy to state the isolation and quarantine measures that should be used in the prophylaxis of measles. Briefly they are: immediate isolation of every case of measles as soon as the disease develops and maintenance of isolation until the exanthem has faded, ten to fourteen days after onset, depending upon the duration of the active stage of the disease; immediate isolation of *all suspected cases* until the diagnosis is established; quarantine of susceptibles known to have been exposed until the incubation period is safely past. The practical application of these measures, however, is often very difficult for reasons that have already been referred to. Probably the most difficult to contend with is the frequent failure to consult a physician until the exanthem appears.

The immediate and rigid isolation of every case of measles as soon as the diagnosis is made and the maintenance of isolation until danger of transmitting contagion is past present no great difficulties in practice among families with adequate housing facilities. If the patient is to be treated at home a room should be selected from which other members of the family may easily be excluded, preferably on the top floor. No one but the actual attendants should be allowed to enter. It is especially important that isolation be established at once as only a few moments' exposure may result in transmission of the disease. It is thoroughly understood that those in attendance upon measles should not take the chance of carrying the disease to others although this is a very rare occurrence. In order to avoid this possibility it is necessary that attendants thoroughly scrub their hands with soap and water after coming in contact with a patient with measles and that they refrain from coming into intimate contact with children susceptible to the disease immediately after having seen a case of measles. It is furthermore desirable that a gown be worn by the attendant to avoid contamination of his clothes.

As to disinfection of the room, clothing and other articles at the termination of the isolation period, no elaborate measures of sterilization are necessary, since the virus of measles remains viable only a comparatively short time after it leaves the human body. The windows should be opened and everything that has come in contact with the patient should be uncovered and exposed, preferably in sunlight for six to twelve hours. Disinfectants are not required in so far as the virus of measles is concerned, although their use may be highly desirable for the destruction of other organisms when complications have occurred.

When facilities for effective isolation are not available in the home, a patient with measles should be sent immediately to a hospital for infectious diseases, provided a satisfactory one is available. Provision for the establishment of effective prophylactic measures in children's hospitals is a matter of the greatest importance, since hospital epidemics may be attended by a relatively high mortality. This fact is not as widely appreciated as it should be. In order to cope successfully with measles, hospital wards should be provided with the cubicle system, the personnel should be sufficiently adequate and properly trained in the conception of medical asepsis in going from patient to patient and there should be sufficient observation rooms.

Immediate isolation of all suspected cases until the diagnosis is established is an imperative measure if the spread of measles is to be checked. It is, however, a much more difficult problem than the isolation of cases in which the diagnosis of measles is established. Opposition on the part of parents to what they consider an unnecessary disruption of the household, the impracticability of immediately sending to a hospital children in families where isolation facilities do not exist in the home from an economic point of view if no other, and the tendency of the physician to temporize and his disinclination to institute rigid isolation measures until he is sure of the diagnosis, all contribute to the difficulties of the situation. A more resolute attitude on the part of the profession should lead to more effective limitation of the spread of measles than now exists, not to mention the probable prevention of the transmission of other infections which may result. The methods of isolation that should be employed in suspected cases do not differ from those described above.

Quarantine of susceptibles known to have been exposed until the incubation period is safely past presents even greater difficulties than the isolation of suspected cases. The number of cases of measles in which knowledge of exposure has existed prior to the onset of the disease is difficult to determine. Certainly in a considerable number measles occurs without knowledge of the time or place of exposure. On the other hand, in family, school and institutional outbreaks, the fact of exposure is usually known. Under these conditions the measures to be employed necessarily vary with the circumstances.

When measles occurs in a family the safest procedure is to quarantine all *susceptible* members of the family for fourteen days after the *last* possible day of exposure. Members of the family who have had measles need not be quarantined nor is it necessary to exclude from the house others who have had measles since a second attack is extremely uncommon. The effective institution of this measure is of course difficult, particularly among the uneducated and poorer classes, and often the best that may be hoped for is the exclusion of exposed susceptibles from school.

Special problems present themselves when measles breaks out in schools or similar institutions. Closure of schools, except under exceptional circumstances, is not a very satisfactory method because of the enormous waste of school time involved, particularly with respect to children who have already had measles and are for practical purposes immune. If an accurate record of all pupils is kept on file so that the susceptibles and immunes are known, fairly satisfactory results may be obtained by the exclusion of all children who have not had measles until the fourteenth day after the occurrence of the first case. The parents of the children excluded should be notified of the exposure and the children should be isolated at home during the period of exclusion from school. The important point is prompt action when the first case occurs. That exclusion of susceptibles as outlined above is a safer and more effective procedure than daily inspection for the first signs of measles, there can be little doubt. Even in the most skilled hands there are too great chances of error for the latter method to be successful. That it is very difficult to convince parents that it is necessary to carry out quarantine measures in the case of measles is fully recognized, but this should be no deterrent to every effort to make the measures as effective as possible.

Specific Prophylaxis.—The difficulties involved in the prevention of measles by isolation and quarantine measures have led to numerous efforts to develop a practical method of immunization against the disease. This may theoretically be accomplished by: (1) passive immunization with an antimeasles immune serum; (2) active immunization by inoculation of the virus of measles; (3) combined active and passive immunization with virus and immune serum.

The first of these methods, that is, passive immunization of exposed susceptibles with immune serum obtained from convalescent cases of measles, has been extensively tried in recent years since Richardson and Connor first demonstrated that measles could be prevented by this procedure. Degkwitz, Kutter, McNeal and others have reported successful prevention in large series of susceptible children who had been exposed. Degkwitz found that the optimal time to bleed the convalescent donor is between the seventh and fifteenth day after the disappearance of the fever. Complete protection was afforded the recipient by the injection of 3.5 c.c. of serum before the end of the fourth day after exposure, but, if the injection was delayed until the sixth day after exposure, double the dose was required. If less than 3 c.c. was given not later than the fourth day, the incubation period was prolonged and the disease was very mild.

By the seventh day after exposure, large amounts of serum failed to protect or to lessen the severity of the attack.

This method of immunization and prevention should be of great practical value in family and institutional outbreaks, and, as McNeal has pointed out, recommends itself most highly for the prevention of measles during the period of danger, between the ages of five months and six years, especially in tuberculous children and in those physically below normal.

The serum should be collected with the usual aseptic precautions, should be kept stored in the icebox until used, and should be injected intramuscularly in a single dose of 4 c.c. to 8 c.c., as soon after exposure as possible. The immunity conferred is probably a temporary, passive immunity in most cases, though Degkwitz and Kutter suggest that under certain conditions a more or less permanent active immunity may develop.

That the method is not universally applicable because the source of the immune serum is limited and because the fact of exposure is frequently not known is obvious. No practical method of active immunization, however, has been developed at the present time.

TREATMENT

Since there is no specific remedy which will either cure or shorten the course of measles, treatment is directed toward the relief of symptoms, the prevention of complications, and the treatment of complications when they occur.

General.—The general care of the patient is a matter of considerable importance. The patient should be put in bed from the very onset of the disease, even though the prodromal symptoms may be comparatively mild. Much harm may be done by allowing patients to be up during this period. Furthermore, patients should not be allowed to get out of bed until convalescence is established. Insistence upon these two measures will frequently do much toward lessening the severity of the symptoms and preventing the development of complications.

The room in which the patient is placed should be large and well ventilated. While it is important that the patient should be protected from direct drafts, it is equally if not more important that an adequate supply of fresh air be provided for. The temperature of the room should be between 65° and 70° F. when possible; the air should be moist. Extremes of temperature and dry air are prone to increase the severity of the respiratory tract symptoms. Because of the photophobia the bed of the patient should be so placed that the light does not strike directly on the patient's eyes. The former custom of excluding all light and fresh air from the room in which a patient with measles is treated is not desirable.

The toilet of the patient is important, especially with respect to the eyes and the mouth. The eyes should be cleansed or irrigated night and morning with boric acid solution. The mouth should be frequently washed with a weak solution of bicarbonate of soda or boric acid. In infants and young children sprays may be employed, gargles being used in older subjects. It is important to recognize that these procedures are for the purpose of cleansing and that all irritant antiseptics such as iodin and silver nitrate should be avoided. The skin should be kept clean by a daily sponge bath, care being taken that the patient is not unduly exposed. The temperature of the water may be hot, warm or cool, as the patient desires. Cold baths should be avoided.

The diet should not be excessive because of the tendency to diarrhea and enteritis which exists in measles. On the other hand, it is important, especially in children, that adequate nourishment be given. Milk, eggs, toast, broths, rice, jellies, and ice cream are suitable. During the febrile period water should be given at frequent intervals. With the onset of convalescence the diet may be gradually changed to a normal diet by a week after the temperature has fallen to normal.

In mild cases patients may begin to sit up after three to four days of normal temperature. In more severe cases it is desirable to be a little more cautious, since unexpected complications may develop if undue haste in getting out of bed is permitted. In the absence of complications the patient may ordinarily be considered well from seven to ten days after the temperature has fallen to normal.

Symptomatic.—Measles is frequently accompanied by a variety of symptoms which require treatment for their relief. The most frequent and important are those attributable to the inflammatory congestion of the respiratory mucous membrane. Treatment of these is important not only because it adds to the comfort of the patient but also because it diminishes the liability to such complications as sinusitis, otitis media, and bronchopneumonia. The treatment should aim to reduce congestion and allay irritation. For rhinitis and pharyngitis the mucous membranes should be sprayed with a mild alkaline solution for cleansing purposes. To this may be added wintergreen or peppermint flavor if desired. This may be followed by a mineral oil spray containing a little menthol, thymol, or eucalyptol. If congestion is extreme, marked relief may often be obtained by the application of adrenalin (1:1,000). For the inflammatory laryngotracheitis steam inhalations with eucalyptol, menthol, creosote or other similar preparations are valuable for soothing the irritation. At night when it may be necessary to discontinue steam inhalations vaselin containing any of the above ingredients may be rubbed on the chest and throat. If cough is very irritating and persistent, especially at night, it is often necessary to give codein. The value of expectorants is somewhat doubtful, but if secretion is slight and cough non-productive ipecac or ammonium chlorid may be tried.

Nervous symptoms, which are presumably manifestations of a severe infection, need attention when they occur. Irritability, insomnia, and convulsions may develop during the course of measles. Hyperpyrexia frequently accompanies them. For excitement and delirium frequent cool sponges and the application of an ice-bag to the head are useful. The reaction of the patient must be carefully watched and too great depression avoided. For insomnia, hot drinks, cool sponges, and treatment of the cough frequently suffice. If these are not effective a hypnotic may be necessary. For children sodium bromid (0.3 gm.), every two hours or paraldehyd may be used. For convulsions similar treatment is indicated. Chloral hydrate either by mouth or by rectum and very rarely morphia may be required. The temperature should not be treated unless it goes above 106° F. In such cases cool sponges should be used.

Diarrhea is sometimes a troublesome symptom and should be treated as it may lead to complicating enterocolitis if neglected. Warm applications to the abdomen and restriction of diet to boiled milk or milk with limewater, cocoa, rice, toast, or similar non-irritating foods with little residue are indicated. A preliminary dose of castor oil may be desirable if the bowel is overloaded, but it should not be given unless necessary. If diarrhea persists, irrigation of the large intestine with hot water, astringents, and in very severe cases small doses of opium or an opium and starch enema may be used.

Complications.—The most serious aspect of measles is that it predisposes the individual affected to secondary infection with a variety of pathogenic bacteria. The most frequent complication is bronchopneumonia which is responsible for about 90 per cent of the deaths in measles. Otitis media, mastoiditis, sinusitis, laryngitis, cervical adenitis and ileocolitis are not infrequent. Latent tuberculosis may be aroused to activity. Blepharitis, keratitis, corneal ulceration or panophthalmitis may accompany the disease. Meningitis, noma, osteomyelitis and arthritis are complications which occasionally occur. The incidence of these complications is greater among children under four years of age than among older children and adults. It is greatest among patients treated under unhygienic or crowded conditions, especially in institutions, irrespective of age. In view of these well-established facts it follows that the most important thing to be accomplished in the treatment of measles is the prevention of complications in so far as this is possible. Fortunately we possess methods which if rigidly adhered to are fairly efficient.

Prophylaxis.—In order to apply preventive measures intelligently it is necessary to know the causes of complications and the manner in which they arise. Extensive bacteriological investigations of the commoner complications of measles have shown that the organisms most frequently associated with these complications are Streptococcus hemolyticus, pneumococcus and Bacillus influenzæ. Of these streptococcus is probably the most frequent and most important. Theoretically secondary infection of the lungs, ears, paranasal sinuses and so forth might arise in persons innocently harboring streptococci or other bacteria in the mouth when resistance is lowered by the occurrence of measles. In this case infection would be autogenous and little could be accomplished in the way of prevention other than the general measures outlined above for the treatment of measles. On the other hand, complications might be due in large part to invasion of organisms from outside the body, that is, to contact infection. Should this be so, it should be possible by guarding the measles patient against outside sources of infection to reduce greatly the incidence of complications.

The well-established fact that complications are much more frequent when measles patients are treated in groups in institutions than they are in patients treated in private homes is strong presumptive evidence in favor of the view that complications arise by spread of infection from patient to patient, either directly or indirectly, much as puerperal infection or erysipelas used to do before the institution of aseptic measures in the management of these diseases. More direct and conclusive evidence has been provided by careful studies of the incidence of hemolytic streptococci in the throats of measles patients, the dissemination of streptococci in measles wards and the relation of the development of streptococcus complications to the streptococcus carrier rate. Cole and MacCallum have shown that hemolytic streptococci become rapidly disseminated among measles patients when treated in groups in hospital wards. On admission they found that 11.4 per cent of cases had positive throat cultures, after from three to five days in the ward 38.6 per cent, and after from eight to sixteen days 56.8 per cent showed hemolytic streptococci.

In a similar but more extensive study of 867 cases of measles, Small found 4.2 per cent carriers of hemolytic streptococci on admission. After one week in hospital 10.9 per cent showed positive throat cultures, after three weeks 26.2 per cent, and after four weeks 33.1 per cent. Of particular significance is Small's observation that the increase in carriers occurred conspicuously in certain wards and that streptococcus bronchopneumonia, otitis media and mastoiditis occurred largely in these same wards in which active dissemination of streptococci took place. Further evidence that complications arose from contact rather than autogenous infection was found in the observation that streptococcus complications arose only among patients who acquired the streptococcus after admission to the hospital, while those carrying streptococci at time of admission developed no streptococcus complications.

Since it has been definitely established by observations such as those cited above that contact infection, direct or indirect, is an important cause of the more serious complications of measles, it is essential that measles patients be protected from all outside sources of infection with hemolytic streptococci, pneumococci or other pathogenic bacteria. It has been pointed out by Opie, Blake and others that the most important sources of streptococcus complications are patients acutely sick with streptococcus infections such as bronchopneumonia, tonsillitis, and otitis media. The same undoubtedly holds with respect to other infections caused by pneumococcus, B. influenzæ, staphylococcus, etc. These organisms are readily transmitted from one individual to another by direct contact, by droplet infection, and by contaminated hands of attendants.

In view of these facts certain definite measures are essential in the management of patients with measles in order that the incidence of complications may be reduced to a minimum. These measures are: (1) individual isolation; (2) medical asepsis.

Individual isolation of patients with measles, though widely recognized as an effective measure for the prevention of complications, is not universally used either in the home or in the hospitals. It should be insisted upon, however, if the best results are to be obtained. When two or more children in the same family are sick with measles they should be placed in separate rooms whenever possible. If separate rooms are not available and it becomes necessary to have two children in the same room, the beds should be placed as far apart as the size of the room permits and a screen should be interposed halfway between the two beds as a constant reminder that a rigid individual isolation technic must be maintained with respect to all articles or persons that come into contact with the patients. The same rigid isolation is even more important when measles patients are treated in hospital wards because the sources of secondary infection are greatly multiplied. The installation of permanent partitions or cubicles in wards devoted to the care of measles patients is the only effective method of providing individual isolation. No measles ward should be without them.

A rigid aseptic technic in the management of measles patients is of the utmost importance and must go hand in hand with individual isolation if complications are to be prevented. This is of course especially important in hospitals, but almost equally so in the home. Each patient should be provided with his own toilet articles, dishes, linen, thermometer, etc. No articles should be used in common. Any articles contaminated by contact with the patient should be sterilized by the appropriate measures before being used again. Special precautions should be used by physicians, nurses, or other attendants in order to prevent transmission of pathogenic bacteria to the patient. The hands should always be thoroughly scrubbed with soap and water both before and after coming in contact with the patient. Separate gowns for each patient should be provided. The all-too-prevalent custom of donning a gown on entrance to a measles ward and of going from patient to patient without scrubbing up or removing the gown until leaving the ward cannot be too strongly condemned.

From the point of view of prevention of complications, the essential factor in the management of measles is such isolation of each patient that microörganisms cannot be transmitted from one to another or from attendants or others to patients. However perfect the organization of a measles ward and however efficient the aseptic technic in force, it is furthermore desirable that patients with complications be separated as far as possible from those without, so that the accuracy of the measures in force may not be put to too severe a test.

Treatment.—The treatment of the complications of measles does not differ from the treatment of these conditions when they occur independently or as complications of other diseases. The reader is referred to the appropriate chapters.

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CHAPTER IX

GERMAN MEASLES

(*Rubella*)

F. Forchheimer

Revised by George Blumer

Prophylaxis.—Some question has arisen as to the necessity of isolating patients who have this disease. It would seem that a disease in which a fatal issue has so rarely been observed would require no isolation. Certain it is that most authors who have described German measles have seen no mortality, and when it has occurred it has been in hospital practice principally. If there is isolation it should be on account of morbidity, and not on account of mortality. While rubella does not spread as rapidly as measles, probably on account of the longer period of invasion, it does present itself as an epidemic disease. The first large epidemic that came under my observation spared neither large nor small, young nor old, male nor female; the morbidity relatively great, the mortality nil. Most of those affected attended to their vocations, including some physicians who continued to visit their patients. The few that remained in the house were kept there by troublesome eyes which prevented them following their work, general malaise, fever, or cough, and then it was only a few days—at all events not long enough certainly to render themselves free from contagion. Under these circumstances it is not strange that no isolation takes place; when the patient is not sufficiently ill to stay in the house, it is difficult to keep him there except by force or reason. Neither force nor reason are required in a disease in which there is practically no danger to life. There *is* no reason except an economic one; the question is how much the state loses by permitting these patients to go about. The individual gains by attending to his work, the state loses by his spreading the disease. Rubella epidemics are not frequent; a large number of individuals enjoy immunity; predisposition is not so great as in measles, and one attack produces protection against further attacks. Compared with measles, it will be seen that we are dealing with a different problem in rubella prophylaxis. In the former, on account of mortality and sequelæ, strict prophylaxis; in the latter, only exceptional prophylaxis. This exception is found in young or old in whom rubella might turn the scales from life to death. If necessary, the patient should remain isolated for two weeks, and until desquamation is completed, according to those authors who touch upon this part of the subject at all. Judging from analogy with measles, the patient would be free from contagion after the first days of the desquamation has set in. Certainly it would be an injustice to carry this out except in so far as the person to be protected should continue to remain away from the patient as much and as far as his relations to him will permit. Until we know more about this whole subject, this seems the fair attitude.

Finally, the difficulty of prevention must be considered. A disease with a long period of incubation, a period of invasion so short that it can be neglected, and with contagiousness as sure as the symptoms appear, can not be easily kept from spreading.

Treatment.—This is hygienic and medicinal as in measles. Frequently, none is required. In the severer cases the patient should be kept in bed during the eruption and for two or three days after this. Where fever is present, a light diet is demanded. Many of the patients have no fever, do not feel sick and resent active treatment. The urine should be carefully examined as nephritis has occasionally been reported as a complication. The treatment in such cases is the same as for the acute nephritis complicating other exanthemata.

CHAPTER X

VARICELLA

JOHN RUHRÄH

REVISED BY GROVER F. POWERS

Synonyms.—Chicken-pox, also formerly water pock, glass pock; Latin, varicella; French, la varicelle, la vérolette; Italian, ravaglione, morviglione; Spanish, viruelas locas; German, Varicellen, Windblattern, Wasserpocken, Schafpocken.

Definition.—Chicken-pox is a specific infectious disease usually characterized by a slight fever, a slight disturbance of the general system, and a characteristic eruption beginning as a papule and rapidly changing into a vesicle which sometimes becomes pustular, but which usually dries and forms a brownish scab, which falls off in from ten days to three weeks after the beginning of the disease. There are exceptional cases in which the eruption is hemorrhagic and sometimes gangrenous. Occasionally troublesome complications arise, consisting chiefly of pneumonia, bronchopneumonia, and nephritis. Sometimes skin infections or abscesses are noted.

History.—It is questionable whether the disease was differentiated by the ancients, but it probably was not; although Hesse, in his voluminous monograph published in 1829, states that there are some authors who believe that the older writers gave good descriptions of the disease. This rests, however, on rather slender authority.

It was separated from small-pox by Vidius in 1626, and Duncan Liddle of the same period. Fuller, in 1730, and Heberden, in 1767, gave very clear descriptions of the disease. The question of the identity of the disease and small-pox has been, from the early part of the eighteenth century almost until the present time, a matter of more or less acrimonious debate, the famous dermatological school of Vienna under Hebra declaring the identity of the two diseases. The renewed experience of the severe epidemic of 1870 and 1873, however, again caused the profession to take the view of the non-identity of the two diseases, and I am not familiar with any writers of any importance of the more recent times who have questioned this. It is a question one may regard as definitely settled, although it will doubtless be reopened from time to time. It is an important one, and the reasons that one may adduce for the non-identity of the two diseases are that small-pox does not protect from chicken-pox, nor does chicken-pox from small-pox; and, indeed, it is possible to have both diseases at the same time. This has been noted by various observers, Schamberg among others. In cases of chicken-pox admitted to the small-pox hospitals through mistaken diagnosis, the chicken-pox patients, unless protected by vaccination, may take small-pox, while the small-pox patients, unless they are protected by a previous attack of chicken-pox, are liable to contract that disease. There is some evidence to suggest that varicella and herpes zoster have a common etiology.

Incubation and Transmission.—Inoculation experiments with the serum from the vesicles usually do not transmit the malady, although a few observers have been able to transmit it in this way. The incubation period in these cases is about ten days; and a general eruption is obtained and not a localized vesicle, as one might suppose. Nothing definite is known as to how the disease is transmitted from one individual to another, nor what is the portal of entry; but that infection takes place nearly always by direct or close contact seems to be well established. The possibility of transmission begins with the first symptoms and lasts perhaps until the crusts have separated, or nearly until this time, so that a safe rule for the isolation of patients is until the body is free from scabs and crusts. There is sometimes gangrene or skin infections which may be prolonged over considerable periods, but in these cases the patient is not to be regarded as a source of danger in transmitting the disease, after the uninfected vesicles have healed and the scabs separated. The disease is rarely carried by a third person, and very rarely by fomites, and then only when the exposure takes place shortly after the fomites have left the patient, the virus, whatever it is, seeming to be easily killed by a short exposure to light and air. This is just the opposite from small-pox, in which the virus is resistant. The incubation period is usually from thirteen to seventeen days, and, while some authors place the extreme limits as eleven days and four weeks, respectively, it may safely be asserted that there is little or no danger of the disease developing after three weeks have elapsed after exposure. If the day of the first contact with the disease is known, there is, perhaps, no objection to allowing the child to go about freely for the first ten days. After that, during the period in which the disease is apt to develop, the child should be kept away from other children.

Susceptibility and Immunity.—The incidence of the disease is greatest during the first ten years of life; the disease is rarely seen in adults, perhaps for the reason that almost every one has had the disease during childhood. No age, however, is immune, and the disease may be seen at times in old individuals. Immunity conferred by one attack is usually quite perfect, although second attacks have been reported, and Gerhardt has reported as many as three attacks in the same individual. Varicella occurs with other diseases and runs its course uninfluenced, except that in some instances it may perhaps be more severe. Attacks have been noted after vaccination. Vaccination done immediately before or at the time the child is suffering with chicken-pox takes, as in a normal child, and seems to have no influence whatever on the course of the disease.

Prophylaxis.—The prophylaxis of the disease consists chiefly in isolation. The disease is usually so mild and of such benign character that many physicians and most parents make no effort to prevent spread of the disease. It should be remembered, however, in this connection that fatalities may result, that gangrene may occur at times, even in children who are previously healthy, and that, in the very young and very weak children, the disease itself may be a source of danger; or it may so lower the resistance that other infections may be a source of danger to the children. Isolation in schools, hospitals, and other institutions should be rigorously carried out. Chicken-pox and measles have the distinction of being the most difficult of all diseases to isolate perfectly, as it would seem that the virus is capable of passing through the air, perhaps on flying particles of dust, for short distances, so that, unless a very rigorous technic with suppression of dust is secured, the disease is very liable to spread (see Measles). Isolation, where there is a free air space around the isolation ward, is comparatively easy. In private houses isolation is practically of no avail unless the most rigid technic is observed. This consists in isolating the patient and nurse, and in not permitting the other children to come near the isolation room. Isolation which is not rigid is of no value whatever, and, if undertaken, only serves to weaken the faith of the public in the value of attempting to prevent the spread of disease by a method of great importance in the prevention of scarlet fever and diphtheria.

Prophylactic inoculation by the cutaneous (Kling) and intravenous (Hess and Unger) routes with the serum from fresh varicella vesicles has been practiced by several investigators. Protective immunization has been reported but the results certainly have not been uniformly successful.

Treatment.—The treatment of the patient is usually a matter of considerable ease. In many patients nothing whatever is required. It is a good plan to give a mild purge at the outset, and, if the patient has *fever,* he should be confined to bed. In some instances the fever is high and the general symptoms severe. The fever is usually best controlled by cold sponging, tepid baths, and the use of ice-bags. In bathing the child great care should be taken not to rub the vesicles. Sometimes equal parts of alcohol and water are more efficient and will reduce the temperature in a shorter time than water alone, and are useful in lessening the danger of secondary infections. Alcohol and water for sponging may also be advised if there are many pustules. If the cold applications and sponging do not relieve the *nervous symptoms* accompanying the fever, small doses of antipyrin or acetphenetidin will be found useful.

The Eruption.—In the case of girls the *scarring* is a matter of considerable moment. It should be borne in mind that chicken-pox does not scar unless the scabs are picked off and are not allowed to fall off naturally, or when the vesicles become pustules. It is the rule, although not an invariable one, that a pustule will leave a scar consisting generally of a small punched-out typical cicatrix. If two or three of these happen to run together, or if the pustule becomes large, the resulting scar may be quite unsightly. As a rule, most of the chicken-pox eruption is on the parts of the body not exposed to light, just the opposite from small-pox, the hands, wrists, face, and neck having comparatively few vesicles. But this is not always the case, and it sometimes happens that they are very numerous on these parts. To prevent scarring, *protection from the light* is thought to be of value. Placing the child in a room in which all the actinic rays have been excluded by the use of red glass, or, perhaps, in a more practical manner, by the use of reddish-yellow curtains, which may be had for a very small outlay, may be tried. Or, if this is not possible, keeping the room semidarkened may be recommended as a substitute; and the wearing of loose gloves and a loose mask over the face may also be tried. In using a mask it should be changed sufficiently often to avoid the danger of infection from its being soiled. As a rule, with proper care, the scarring can be reduced to a minimum, except in the case of young children who are apt to infect the vesicles by scratching. In these, as in other patients, if the tendency to scratch is irresistible, the hands should be restrained. It is well in all cases to pay particular attention to the *cleanliness of the hands,* to have the nails cut short so as to avoid scratch marks. If there is any special tendency for the eruption to become infected, the pocks may be painted with tincture of iodin, which may be diluted one-half with alcohol in children with very delicate skins, or the painting may be done with a 4 per cent solution of picric acid.

Itching is the most troublesome symptom of all, and in some patients is very intense. This may usually be controlled by various means. The use of baths or sponging with hot water, to which bicarbonate of soda has been added in the proportion of a teaspoonful to a pint, acts sufficiently in many cases. Dusting with talcum powder or any other bland powder is of great service, and local applications, where the above measures do not suffice, of various antipruritic remedies may be tried. Of these menthol and carbolic acid are the most effectual; the latter may be applied either in the ordinary carbolated vaselin or as a mixture of carbolic acid and glycerin. Menthol is best applied in a 1 or 2 per cent alcoholic solution or in liquid albolene. A solution of borax in hot water and 2 to 5 per cent of resorcinol may also be tried. Sponging with solutions of alum, 1 to 5 per cent, is frequently of value. Ichthyol in the form of an ointment is often quite effectual, but it is a dirty application and should not be used unless other methods fail. In severe cases, where the itching disturbs the rest of the child, the internal administration of antipyrin with or without the addition of codein sulphate, or sodium bromid, is of great benefit. In pruritus about the anus and vulva, ointments containing balsam of Peru may be prescribed, or ointments containing 1 or 2 per cent of salicylic acid.

The *mouth* is sometimes inflamed. This is due to the presence of vesicles on the mucous membranes, which sometimes leave ulcers. Usually a simple, unirritating, antiseptic mouth wash is all that is needed. If the ulceration tends to spread, the application of burnt alum may be resorted to, and occasionally cauterization with lunar caustic may be advisable. The genitalia should receive especial care, consisting of great cleanliness. If there is any tendency to itching or to infections, some mild antiseptic ointment should be applied. This, perhaps, reduces the danger of severe infections, and possibly of gangrene. If abscesses or local skin infections occur, they should be treated by ordinary surgical methods. A wet dressing with a saturated solution of boric acid and 25 per cent alcohol is one of the most efficient means of controlling these. If crusts form, due to the drying of pus, they may be removed after softening with olive oil or vaselin. The other complications are treated according to the usual methods. The *hemorrhagic eruptions* are best let alone, although, if there is itching, there is no objection to using the methods referred to above. Antiseptic dressings may be applied when there is gangrene of the skin. I have little faith in any therapeutic measures in the treatment of *gangrene* of the skin in children, although this is a personal opinion based on the observation of not very many cases. Almost all that I have seen have proved uniformly fatal, no matter what was done.

Diet.—The diet in chicken-pox should be light during the febrile stage. If there is pain on swallowing, the food should be liquid and given cold.

Convalescence.—During convalescence sunlight and fresh air, cod-liver oil and iron are needed, especially if anemia follows. In the children of the well-to-do, where the child does not rapidly regain its strength, a change of climate may be advised.

CHAPTER XI

SMALL-POX

JOHN RUHRÄH

Synonyms.—Latin, variola; French, la variole; German, Blattern or Pocken; Italian, vajuôlo; Spanish, viruelas.

Definition.—Small-pox is an acute specific infectious disease characterized by a sudden onset, an initial fever lasting three or four days, followed by a characteristic eruption which passes through the stages of papule, vesicle, and pustule, and finally dries and drops off, very often leaving more or less typical scars. The fever usually ceases or becomes intermittent on the appearance of the eruption and recurs when the vesicles change into pustules.

History.—Small-pox has been known from very early times, particularly in China, and, while there is every reason to believe that it was present in the various countries, the older writers did not give very clear descriptions of it. About the first century, however, there can be little doubt of the presence of the disease, and numerous widespread and severe epidemics have been reported. The first accurate description is perhaps that of Isaac, but the best of the early descriptions is that of Rhazes, who lived in Bagdad about A.D. 900. The disease was at first confused with measles, from which it was distinguished by Avicenna (980-1037), and Sydenham finally gave such a description as to lead to the separation of the two diseases, and he also changed the treatment of the disease into what might be regarded in the main as that of the present day, in that he believed in plenty of fresh air and the use of cooling applications, in place of sweats and the numerous other methods of treatment previously in use. The disease was probably imported from the old country to America early in the sixteenth century, and there were numerous epidemics which exterminated many Indian tribes, and reduced others to a handful of individuals. One thing which is often overlooked in thinking of small-pox is the fact that in prevaccination days every one had the disease, and at that time it was a disease of childhood, the adult population consisting of those individuals who had survived the attack which, Lettsom states, occurred almost invariably before the seventh year. From the descriptions of writers of that period almost every one was more or less pock-marked and the disease was regarded as a disagreeable necessity, much in the light that we now regard measles.

Susceptibility.—Susceptibility to the disease is quite general and infants do not seem to enjoy the natural immunity to it which they show toward most infections. The disease is known to affect infants in utero when the mother has the disease, and young infants exposed to the disease almost invariably take it. There are, however, a few individuals who seem to be naturally immune. This number is perhaps very small; indeed, curious variations in the susceptibility to small-pox exist, just as the same variations are noted in other infections. An individual may be exposed and not take the disease at one time and become infected at a subsequent exposure. One attack usually confers an *immunity* which lasts for the remainder of the individual's life. Second attacks may, however, occur, and there are a few undoubted instances of these on record. Many of the second attacks, however, are due to mistakes in diagnosis, which, in regard to small-pox, are exceedingly common. During two years' service in a hospital which received small-pox cases, I saw every disease that could possibly be mistakenly diagnosed as small-pox. Jenner was a great believer in the immunity conferred by one attack and, while his views may have been influenced by his advocacy of vaccination as a means of producing the immunity in another way, it would seem that he was not very far from the truth.

Small-pox may be present at the same time with other infectious diseases. There is a prevailing impression that the disease is more common in dark-skinned races, especially in negroes, but this is perhaps due to the fact that these races are not so well protected by vaccination. The disease is one which occurs in temperate climates in the winter months, and almost all of the cases are during cold weather. In tropical countries it is said that the worst cases occur during the hottest months.

Organism.—The organism causing small-pox is now thought to be an organism known as the Cytorrhyctes variolæ. These bodies, which have been studied in the skin, were first described by Weigert in 1874, and were supposed to be parasites by Renault in 1881. In 1892 Guanieri gave the first clear description of what he believed to be a parasitic protozoön, and the cause of vaccinia and small-pox. These bodies have been studied by numerous observers, among whom may be mentioned Councilman and his associates, and most of the reports that have been made tend to confirm the views of Guanieri. This subject, however, is one which is worthy of further study.

Infective Period.—It is extremely doubtful whether small-pox is transmitted during the stage of incubation, and it is safe to assert that if one takes into account only the ordinary means of transmission there is no danger from patients during this stage. The danger begins from the beginning of the symptoms and lasts until all of the scabs have separated. There is perhaps less danger during the last stages of the disease, but there seems to be no doubt that the dry scabs may contain the infectious material and so be a definite source of danger. It should also be borne in mind that the infectious material is present in cadavers and may remain in them apparently for long periods of time; so that the disease occasionally results from such bodies finding their way into dissecting rooms, or from the exposure of small-pox corpses in other ways. Morgue attendants have contracted the disease in this way.

Transmission.—There is still considerable discussion of the ways in which the small-pox virus is transmitted. There can be no doubt that almost all of the cases are the result of direct contact with individuals having the disease. Small-pox may be of such a mild nature as to be almost unrecognized, and an individual with a light attack of the disease going about and mingling freely with other people may cause a large number of infections which would be thought to be due to fomites, aërial transference, or to some other means of acquiring the disease. The disease may be carried in the discharges from the patients suffering with it and also on fomites, although the danger of this is slight if reasonable precautions are taken.

There has been a great deal of discussion on the subject of whether the disease may be transmitted through the air or not, and I believe that aërial transmission, where it does occur, is accomplished by means of infected dust, so that if dust is suppressed aërial transmission need not be considered. Most of the evidence which has been adduced in favor of aërial transmission is from English sources, and consists merely of the fact that large numbers of cases of small-pox have been found in the neighborhood of small-pox hospitals; but the fact that these infections may easily have been due to direct contact was not taken into account. The experience in modern hospitals with appropriate technic seems to prove rather conclusively that the disease may be easily confined by using simple precautions. The disease may be carried on the clothing or person of a healthy individual who has been exposed to the disease, although this is probably less frequent than has hitherto been supposed. Flies and other insects may in some instances carry the disease, although there is no direct evidence to substantiate this. When one sees flies crawling over small-pox patients, especially when the disease is in the purulent stage, and the pustules have ruptured, the possibility that flies may be a means of transmission becomes apparent. In the temperate climates most of the cases occur during winter, so the fly does not, as a rule, in this region play any very distinct part in the transmission of the disease. The disease may be transmitted by physicians and nurses, and yet this danger may be minimized or entirely done away with by the simple application of the same technic as that used in an operating room.

Incubation Period.—The period of incubation varies somewhat, the disease coming on between eight and fourteen days after infection, with the probability of there being some exceptional cases developing both earlier and later. It is usually thought that if sixteen or eighteen days elapse after exposure the patient will not develop the disease.

PROPHYLAXIS

The prevention of small-pox depends, first, on *vaccination,* and, secondly, on *isolation* and *disinfection.* As to the value of vaccination there can be no doubt. If every one were vaccinated and revaccinated until he was no longer susceptible, small-pox could easily be controlled without any further means. As this is not possible, if we except one or two countries, we must still rely upon the assistance of other measures to protect that portion of the community who willfully neglect to take care of themselves.

In order to study the disease *notification* should be insisted upon, and where possible the diagnosis should be confirmed by some one familiar with the disease, as it not infrequently happens that other diseases are mistaken for it, and needless precautions imposed, to the great annoyance of the individuals, as well as the great expense. *Isolation* may be carried out either in the patient's home or in a special hospital. Of the choice of the two methods there can be no doubt that the transference of all cases to a small-pox hospital lessens the danger of an epidemic, inasmuch as it reduces the number of foci of the disease. Where, for any reason, the patient cannot be removed, a strict room quarantine should be insisted upon. This is usually enforced by means of special guards under the direction of the health department. Where the patient is removed to a hospital the question arises as to whether *the other inmates of the house who have been exposed* to the disease should be quarantined, or whether some other measure should be undertaken. As a period of quarantine for sixteen or eighteen days entails great loss and also causes those so detained to take every possible means to evade isolation, it is perhaps better to vaccinate all those exposed, using by preference three or four separate inoculations with different varieties of virus, so as to avoid, as far as possible, the vaccinations not taking from the use of sterile virus. These individuals should then be allowed to go about, but inspected daily or even twice a day, so as to be able to isolate them promptly should any symptoms of the disease make their appearance. The room or rooms that have been occupied by the small-pox patient should be disinfected.

A small-pox hospital should, if possible, be of modern construction, so that the patient may be made as comfortable as possible. As a rule, small-pox hospitals are hospitals in name only, and consist of barnlike structures with few or no conveniences. The hospital should be away from the center of the community, but at the same time it should not be so far away as to be inaccessible. A building surrounded by a fair amount of lawn should be chosen, where this is possible. The most important feature about the hospital should be the *suppression of dust,* which is usually easily accomplished by washing the floors and woodwork, or by using some of the modern oil preparations for the laying of dust. The *discharges* of the patient should be received in vessels containing carbolic acid, chlorid of lime or bichlorid of mercury, and a sufficient length of time should be allowed to elapse before they are poured out to permit of thorough disinfection. Where it is possible, and it practically always is, a small furnace should be erected, and all *excreta* and *waste* should be burned in this. This is the most satisfactory, the cheapest, and the safest method of the disposal of infectious material. *Bedding* and *clothing* should be disinfected either by boiling, allowing half an hour exposure to boiling water, or exposure to live steam. *Mattresses* should be disinfected by live steam under pressure, and where this is not possible the mattresses should be burned. The articles which are sent to the laundry may be sterilized by an immersion for several hours in carbolic acid, 4 ounces to the gallon, or zinc chlorid, 2 ounces to the gallon; or they may be sterilized by boiling, and at least half an hour's time should be allowed for this. *Nurses* and *attendants* should be isolated with the patient, and under ordinary circumstances should not be allowed to leave the hospital temporarily. Where it is desired to have them leave temporarily or permanently they should change all of their clothing, disinfect the hair by the use of carbolic acid solutions, and take a bath, either in bichlorid, 1:5,000, or carbolic acid, 1:40. Visitors should not be allowed, but, if under exceptional circumstances they are, they should undergo the same precautions as the attendants. It goes without saying that all persons coming in contact with small-pox patients should be vaccinated.

Physicians should take particular care not to carry the virus upon their clothing or person. This is usually easily avoided by the use of the long gown and a cap for the head. These should be hung in the open air, in the intervals between the visits, and should be frequently sterilized. Where the physician must spend any length of time in the wards the clothing, including the shoes, should be changed on entering, and the hands and face carefully disinfected before leaving. If a gown is worn rubber overshoes should be used to avoid carrying dust or scabs which may be on the floor; or the soles of the shoes should be disinfected on leaving the hospital. By using these means visits may be made to small-pox patients without any fear of transmitting the disease to other individuals, but the technic must be carried out in an earnest manner and in every detail. As long a period in the open air as possible should elapse before making visits to other patients.

The *disposal of the dead* is best accomplished by cremation. Where there is any objection to this the body should be wrapped in a sheet saturated in strong antiseptic solution and buried at least six feet under ground in a situation where it will not contaminate the water supply. Burying in lime is a valuable means of destroying the small-pox virus. Public funerals should be forbidden, and the corpse should not be shipped to distant points, or, where this is done, only under very special precautions for the prevention of the transmission of the disease.

The question of vaccination in order to modify the course of the disease is one of considerable interest, and one about which there is some difference of opinion. If the individual is vaccinated in the first two days after exposure, in most instances, if the vaccination takes, the disease will not develop. The results of vaccination in this period are better where the individual has been previously vaccinated in childhood, and it may be regarded as an almost certain preventive of the disease. A certain number of individuals so vaccinated may contract the disease, and this is apparently due to differences in the susceptibility. Individuals vaccinated before the fifth day, while nearly always protected, will sometimes develop the disease, certainly much more frequently than those vaccinated in the first two days. The protection is greater if the vaccination has been performed previously, as during childhood. Part of the failure to get protection is undoubtedly due to using virus which is no longer virulent, and this may often be avoided by vaccinating three or four times, using different makes of virus. Vaccinations done prior to seven days before the appearance of the eruption of the disease exert a favorable influence on its course, if the disease develops. The malady is apt to be lighter and the mortality less. Vaccinations done during the last seven days of the incubation period exert very little, if any, influence on the course of the disease, and vaccinations done at the appearance of the eruption are absolutely of no value, for, while the vaccination may take, it runs a course independent of the small-pox.

TREATMENT

The treatment of the disease may be divided into: the treatment before the eruption becomes pustular, the treatment during the pustular period, and the treatment during convalescence.

Anything which may make the patient more comfortable will exercise a favorable influence, and so tend to lessen the mortality. Of very great importance is sufficient fresh air. The *ventilation* in the wards should be carefully looked after, and, wherever possible, the *temperature* kept at 68° F. or 70° F., and the air of the room changed frequently by opening the windows. The *bedding* is important because one of the sources of suffering is the irritation of the bedclothes, and the patients usually complain of sticking pains no matter how well they are looked after. The sheets should be frequently changed, and the mattresses should be as comfortable as can be obtained; and, where suffering is great and it is possible to have one, a water bed is of considerable advantage.

Diet.—The diet is a matter of considerable importance. During the first stage of the disease, if the patient has much fever, there is no appetite, and the diet should be liquid, consisting chiefly of milk, broth, or albumin water. It is a good plan to modify the milk by the addition of carbonated water, barley water, or by partially peptonizing it. Buttermilk may be given if desired, and koumiss and similar preparations often make a desirable change. There is usually intense thirst, and this may be relieved by plain water, lemonade, or the carbonated waters. As soon as the initial fever subsides and the patient feels relieved, it is a good plan to have him take as much nutritious food as possible. The reason for this is that there is always a very great drain on the system in consequence of the extensive suppuration, and, unless great care is taken to anticipate this, the patient is liable to lose weight, often to an alarming degree. During this period milk, eggs, chops, steak, rare roast beef, and the more easily digested vegetables may be given in as large quantities as the patient desires.

As the eruption develops and begins to suppurate there is a second period of fever, and at this time a return to liquid diet must be made. It sometimes happens that only a liquid diet can be given throughout the entire course of the disease, owing to the eruption in the mouth and throat interfering with chewing and swallowing. It is exceedingly important to have the patient take a sufficient amount of food. As a rule, the appetite is gone, the patient objects to swallowing, and it may be very difficult to have the nourishment taken. The food should be given at regular intervals, every two or three hours during the day and every three or four hours at night. If the patient is awake during the night the food may be given at two-hour intervals, in case only small quantities are taken, or at three-hour intervals if larger amounts are taken. An attempt should be made to have the patient take at least 3 pints of milk, which may be given plain, peptonized, or with the addition of barley gruel or other cereals, or in the form of milk punch. Eggs may be added to the milk, or egg and sherry, or the old-fashioned Stokes' egg and brandy mixture may be used. Broths of various kinds are valuable, and from 4 to 8 ounces of beef juice, pressed from the fresh beef, may be added to the dietary to advantage. This may be given plain or mixed with milk. When there is *dysphagia* the food should be given cold; and in very severe cases rectal feeding may be attempted, although in small-pox it may not be very successful. The use of 1 gr. of orthoform just before taking food is of great service in alleviating the pain caused by swallowing. Where this does not answer the pharynx may be painted with a 1 per cent solution of cocain hydrochlorid just before the meal is given. As a rule, small-pox patients stand the use of cocain very well. This usually permits the patient to swallow with little or no difficulty. In severe cases alcohol may be added to the dietary to great advantage, and it is perhaps best given in the form of whisky or brandy added to the milk, or with a small amount of glycerin or syrup together with water, so as to avoid the irritating effect on the throat. Milk punch or egg-nog may be serviceable. Port or sherry wine may be used if the patient so desires. As a rule, small-pox patients are greatly benefited by the addition of alcohol, especially in the severer cases. In mild cases and those of moderate severity, under twenty years of age, alcohol is, as a rule, unnecessary.

During convalescence the diet may be increased rapidly, and in the favorable cases there is marked increase in the appetite shortly after the fever subsides. Protein food should be given in great abundance to make up for the loss caused by the suppuration. In cases where the appetite does not return the use of tonics containing strychnia and alcohol is to be advised.

The Throat.—The inflammation in the throat is often the greatest source of suffering, and various demulcent drinks may be given, one of the best of which is flaxseed tea, which has been sweetened and flavored with lemon juice. The mouth and throat require careful attention throughout the disease, and should be thoroughly cleansed with antiseptic solutions, of which 1:4,000 permanganate of potash is one of the best; but diluted peroxid or other mouth washes may be used. Chlorate of potash is often of great service. After the mouth has been cleansed the tongue and gums may be swabbed with a mixture of glycerin, boric acid, and water.

Pain.—In the first stage the most prominent symptom is a pain in the back and head. This perhaps is best relieved by the use of antipyrin or acetphenetidin with or without codein sulphate or morphin. Local applications of heat or of counterirritants should, as a rule, be avoided, as a small-pox eruption over irritated surfaces is nearly always confluent. The pain in the head is often relieved by the use of ice-bags or by cold applications.

Fever.—The fever in the first stage is best relieved by cold pack, cold sponging, or by cold baths. As a rule, the treatment in the first stage presents no special difficulties. The development of the eruption and the changing of the vesicles into pustules bring the patient into the stage in which it is most necessary to take the greatest pains to make him comfortable. At this stage there are numerous things requiring attention. High temperature is best relieved by cold packs or cold sponging. *Cold baths* are frequently recommended, but the difficulty of placing the patient in and out of the tub renders their use almost impossible.

Suppuration and Delirium.—Where there is much suppuration, or where there is delirium, *warm baths* are of great advantage. In the confluent cases, where there is involvement of the skin to a great extent, a continuous warm bath is one of the best means of treatment at our disposal. The patient is placed in a tub on a sort of cradle, and the water kept at a temperature of about 95° F. The patient in a *continuous warm bath* should have a special attendant all the time, and hot water should be added frequently to maintain the temperature; for if it falls to 90° F. or 92° F. the patient, as a rule, begins to feel chilly and becomes depressed. The effect of the warm bath is to lessen the delirium, when it is present, to keep the patient's skin clean, and to prevent the formation of crusts and scabs, and the subsequent suppuration beneath them. As a rule, continuous baths are employed only in the worst cases, and, while many patients so treated die because of the severity of the disease, undoubtedly many cases are saved by their use.

The treatment of delirium apart from the use of the warm bath consists in the administration of a cathartic, which sometimes acts most favorably in lessening the excitement; and the use of bromids, either alone or with chloral or morphin, is recommended.

Sometimes the delirium is wild, the patient attempting to escape from the nurse to commit suicide or to injure others. In these cases some form of restraint is necessary. A folded sheet or a band of canvas over the chest, and fastened to the sides of the bed, is often all that is needed. Occasionally it may be necessary to fasten the patient's ankles and wrists by broad bands of webbing; but this should not be done unless there is very urgent need for it, as the patient's tugging on the restraint is apt to lead to extensive injury to the skin, inasmuch as the eruption is liable to be very abundant on the wrists and ankles, and the movements of the patient serve to rupture the pustules.

Insomnia.—Insomnia is frequently a troublesome symptom, and may be treated by the use of hypnotics, veronal or trional often acting favorably. One or two large doses of whisky or brandy may produce sleep.

The Eruption.—The question of the management of the eruption is one of the most important. In the early stages ointments and greasy preparations should be avoided. Wet dressings of various kinds will be found the most satisfactory means of allaying irritation. Dusting powders, while they do much to relieve the local irritation, tend to the formation of crusts under which suppuration is apt to extend. All sorts of things have been suggested; Welch and Schamberg recommend painting the confluent parts with freshly prepared pure tincture of iodin, or in some cases, where this causes irritation, with the tincture diluted. The painting may be repeated every day or every other day. They claim, under this treatment, to secure an early separation of the scabs and a decidedly lessened tendency to the formation of abscesses and inflammation of the skin in the later stages of the disease. A mixture of 25 per cent alcohol and boric acid is a most useful application; spraying the eruption with alcohol, either alone or with the admixture of other antiseptics, has been advised; the use of sprays of ether and 1:3,000 or 1:5,000 bichlorid has its advocates; the aim in all cases being to keep the skin clean and to lessen the tendency to infection. When the vesicles or pustules begin to rupture, frequently changed compresses over the worst parts serve to keep the skin clean and to remove the discharging pus, perhaps better than any other method. An effort should be made to prevent the pus from drying and forming crusts, as the skin is liable to become very much inflamed under these, and abscesses form in consequence. When the skin begins to crust in the natural evolution of the disease, ointments may be used to considerable advantage, especially those containing antiseptics, as they tend to lessen the suppuration, to keep the scabs soft, and to favor desquamation. The skin should be bathed in warm water several times a day, as this aids the separation of the scabs. After the scabs have all come away, the skin is frequently tender and easily irritated; and it is then that a dusting powder, talcum, powdered starch, or whatever may be desired should be used frequently. The tender skin may also be hardened by the judicious use of alcohol rubs or alum baths. *Erysipelas* occasionally develops, and is best treated by wet dressings of antiseptics; bed sores may be treated in the usual manner; and it occasionally happens that gangrene of the skin may be met with. *Abscesses* should be opened as soon as suppuration is evident, and the opening so placed as to favor free drainage.

Itching is a symptom which causes great discomfort, and as far as possible should be controlled, as it leads to insomnia, increases the nervousness of the patient, and leads to scratching, which tears the vesicles or pustules open, and so renders infections of the skin much more frequent. Various external applications have been suggested for the relief of itching. Spraying with alcohol, with or without the addition of ½ to 1 per cent menthol, is of value; sponging with carbolic acid and water, 1:40, is sufficient in many cases; or the carbolic acid may be applied in the form of an ointment. Salicylic acid is applied either in solution or as an ointment, and ichthyol is an efficient application either as an ointment or diluted with glycerin. During the early stages of the disease ointments are, as a rule, best avoided, although there are times when they may be most useful. Alum baths, 1 to 5 per cent, are of considerable service, and various antiseptics have been recommended, chief of which is bichlorid of mercury, but these are uncertain in their antipruritic action. Dusting powders are of great value in allaying itching, but, as a rule, should not be employed until the last stages of the disease. The scarring is lessened by anything which prevents suppuration, and everything which one can think of has been tried. The application of the tincture of iodin as suggested by Welch and Schamberg is perhaps more effective than any other method. Puncturing the pustules is of little or no value, and most of the other methods in vogue are extremely questionable. There is a prevalent idea that, if the scabs are softened and removed early, the scarring will be less. Welch and Schamberg suggest the use of an ointment containing 2 drams of sodium bicarbonate in 1 ounce of petrolatum as being the most efficient preparation they have found for this purpose. Frequent baths help more than anything else, and the baths should have some antiseptic added, as bichlorid of mercury, 1 : 10,000 or 1 : 20,000, or alum, 1 pound to a tub of water of 450 to 500 liters, or about 1 : 1,000 solution.

The *odor* from small-pox patients is particularly objectionable, and adds considerably to the discomfort of the patient and greatly to that of those about him. It is best controlled by very frequent baths, to which has been added potassium permanganate.

The Eyes.—Of very great importance are the complications affecting the eyes. If the eyes are only moderately inflamed, the frequent use of a boric acid eye wash, and the use of some mild antiseptic ointment to the edges of the lids to prevent their sticking together, are all that is needed. The use of this ointment is of primary importance, as the lids frequently get stuck together, and the pus, finding no outlet, causes pressure upon the cornea, often with rapid ulceration, which may result in the loss of sight or of the entire eyeball. Welch and Schamberg advise the use of nitrate of silver applied to the mucous membrane in cases where there is much swelling or discharge. A 5 per cent protargol solution may be employed instead. Where there is much swelling and chemosis it is important that an outlet be made for the pus. The authors mentioned advise the use of cuts in the conjunctiva, or even cutting the outer canthus, if it is necessary, to enable the physician to inspect the cornea and to provide for free egress of the pus. If the cornea becomes ulcerated, and it frequently does, atropin should be instilled when the ulceration is central, in addition to the frequent flushing with the boric acid eye wash. The flushing should be used very often and the external application of cold employed in the intervals. If the ulceration is about the periphery, eserin sulphate, gr. 1/4 to the ounce, should be cautiously employed. As soon as the pupil is contracted the eserin should be stopped. If rupture of the cornea threatens, the edges of the ulcer should be cauterized, using a very dull red cautery or trichloracetic acid. The use of ointments in the eye is important to prevent the denuded cornea from forming adhesions; and those containing small amounts of yellow oxid of mercury are most frequently employed. Ointments of this drug containing, in addition, small amounts of atropin are of great service in treating the milder degrees of ulceration of the cornea. The treatment of the eye conditions must be carried on both day and night, as in many instances neglect is promptly followed by loss of sight.

Inflammation of the Larynx.—Inflammation of the larynx is a less frequent complication, but one which leads to great suffering. Inhalations, either from limewater or from a dram of compound tincture of benzoin in a pint of water, will be found useful. Menthol may sometimes be added to the latter with advantage.

Edema of the Glottis.—If edema of the glottis comes on the patient is apt to die of suffocation unless tracheotomy is done. But, with the tissues of the neck swollen, tracheotomy may be an operation extremely difficult to perform, and attended by considerable hemorrhage. Inflammation of the tongue is not infrequent. The tongue should be painted with glycerite of tannic acid, and, if the swelling becomes very great, incision may be necessary. The other complications are treated along general lines, and scarcely require special mention.

Red Light Treatment.—This has been in use ever since the time of John of Gaddesden, who suggested the use of red bedclothing, red bed curtains, gargling of the throat with mulberry wine, and the sucking of red pomegranates.

In more recent times red light has been employed extensively, the actinic rays of the sun being excluded by using red glass or red cloth. Würtzen has called attention to the fact that the glass should be tested with a spectroscope to see that it does not admit of the passage of green rays, as much of the red glass on the market deteriorates rapidly and is not very effective; the color of the glass to the naked eye is not a sufficient test. As a rule, the red light is well borne by the patient, but nurses and attendants often find it trying. This is somewhat alleviated by wearing variously colored glasses chosen according to individual preference. There has been a general impression that the exclusion of the actinic rays lessens the amount of the eruption, and particularly lessens the amount of suppuration and the subsequent scarring. Whether or not the red light possesses any therapeutic value should be carefully tested. The most recent reports upon the subject would seem to show that it exerts no influence one way or the other upon the course of the disease.

Potassium Permanganate Treatment.—In place of the red light, bandages saturated with potassium permanganate have been suggested. These are changed three or four times a day for the first few days, until the skin is well discolored by them, and later less frequently. There is a great difference of opinion concerning the value of this method, but it has its enthusiastic advocates, among whom may be mentioned Dreyer, who claims to have obtained satisfactory results from it. In his cases he believed that the amount of suppuration was less, that the patient was more comfortable, and that there was less odor than with the other methods of treatment.

Serum Treatment.—The injection of the serum from a previously vaccinated heifer has been suggested, based upon the fact that, if this serum is used in another heifer, it produces a certain amount of immunity against vaccination. This method of treatment has not been tried in a sufficient number of cases to allow one to give any opinion in the matter. Kinyoun claims to have obtained good results from it.

Injecting serum from persons who have had an attack of small-pox has also been suggested. The amount of serum obtainable has been small and the results up to date negative. The method is not to be recommended in the present state of our knowledge.

Small-pox Inoculation.—Small-pox inoculation has been known from very early times, as it was practiced centuries ago in China, the method used by the Chinese being to stuff the dried small-pox scabs into the nostrils. Inoculation was also practiced in India and by various oriental races, particularly by the Turks. The first communication on the subject in England was made in a communication to the Royal Society by Dr. Woodward about 1714. He reported the work of Emmanuel Timoni, which was subsequently reported before the Royal Society by Pylarini, Russell, and others. It was described by Kennedy in an "Essay on External Remedies," London, 1715, but no particular attention was paid to these communications. The real introduction of inoculation into England was by Lady Mary Wortley Montague, the wife of the Turkish Ambassador.

The method is exceedingly simple and consists of inoculating, usually at the insertion of the deltoid, a small amount of the small-pox virus, generally secured from a vesicle on about the fifth day of its development, although the virus is active if taken at a later period. The pock develops rapidly, minute changes being present as early as the second day. The patient is conscious of the inoculation on the third or fourth day, and there is a small hard nodule surmounted by a vesicle on the following day. The vesicle is well developed on the sixth day and there is considerable inflammation and some pain and tenderness. On the seventh or eighth day there is usually a chill or chills, headache, vomiting, and fever. The inflammatory changes in the arm begin to subside at this time, and there is an irregular area covered with vesicles, and there may be a few vesicles on other parts of the body. Sometimes there are only two or three of these, while in other instances there may be a number, one or two hundred or more. Occasionally a very severe type of the disease is produced, but, with reasonable care, the disease runs a mild course and the mortality has been estimated at about 0.20 per cent. While this is a rather crude method of obtaining immunity, it is attended with no danger as compared to that from small-pox acquired in the ordinary way, and, while it has been superseded, and very properly so, by vaccination, circumstances might arise to render this method a proper procedure, such as a small-pox epidemic in the absence of any vaccine virus. As ordinarily practiced, children were inoculated, and the chief objection that can be urged is that a person so inoculated is capable of spreading the disease just the same as one who has taken it by ordinary methods.

Laboratory Diagnosis.—In some infectious diseases the cutaneous injection of the virus will give rise to an inflammatory reaction in an animal previously sensitized. Jenner noted this, but no attention was paid to it. In 1912, Tieche found that persons who were immune to small-pox would not give a reaction with material taken from varicella cases. He suggested this as a means of differential diagnosis. His idea was that the physician could make the tests on himself or some person previously prepared with vaccine virus. He suggested heating the virus to be used in the test to 70° C. for five minutes in order to avoid accidental infection by syphilis.

Force and Beckwith have applied this method to sensitized animals and studied the effect of vaccine, the contents of the small-pox vesicles, and the chicken-pox vesicles, on the skin of previously vaccinated animals. The virus is injected intradermally. On the day preceding the dose two areas about 5 cm. in diameter are shaved and clipped on the back of a previously vaccinated animal. From 0.05 to 0.1 cm. of material is injected directly into the skin. Within twenty-four hours the reaction appears and reaches its maximum the second day. There is an infiltration of the skin with redness which fades before the infiltration disappears. Typical reactions may be produced by vaccine virus or the contents of small-pox vesicles. This material can be kept for nine days at ice-box temperature and still give the reaction. Chicken-pox virus does not produce any reaction in these animals. The rabbits retain their sensitiveness a long while, some of them for one year after the original vaccination. This may be used particularly in the differential diagnosis of small-pox and chicken-pox and should prove very valuable in checking up the clinical diagnosis.

VACCINATION, THE SPECIFIC PROPHYLAXIS OF SMALL-POX

Vaccination may be described as the production of an immunity for small-pox in man by inoculation with the virus of vaccinia or cowpox. This inoculation is characterized by the production of one or more papules which change into vesicles, become umbilicated, pass into a pustular stage, and finally dry up with the separation of the scab, leaving behind a rather typical scar. Accompanying this are symptoms of a constitutional nature, chief of which are fever and more or less malaise.

Correctly to understand the importance of vaccination and the great benefit which it has conferred upon the human race, it is necessary to bear in mind that, prior to the beginning of the nineteenth century, small-pox was the most widely disseminated and most dreaded disease. The number of deaths caused by the disease was appalling. The population of all countries was made up of individuals who had had the disease, usually in childhood, and who had survived it. Occasionally individuals would not take the disease until late in life, but in a general way the disease was regarded much in the light in which we now regard measles, a disease which almost every one had before seven years of age.

It was estimated by Bernouilli, writing about 1760, that small-pox carried off the thirteenth or fourteenth part of each generation.

The disease was present in all countries practically all the time; but from time to time devastating epidemics would sweep the various continents, leaving in their wake not only a tremendous number of deaths, but a population with scarred faces, blind eyes, and numerous other serious affections.

Pock Diseases of Animals

These diseases bear a very close relation to vaccinia, and, taken altogether with the various changes brought about by inoculation into various animals, form one of the most curious chapters in the natural history of disease. These diseases may be divided into two groups. The first, occurring in epidemic form and also sporadically, is very easily communicated from one animal to the other, the contagious principle traveling apparently through the air; although I believe a careful study will reveal that this transmission through air is more apparent than real, the transmission in such cases taking place through infected dust and infected particles of skin, saliva, etc. A second characteristic of this group is that these diseases are, for the most part, very fatal; and a third common characteristic is that the eruption is general. This group includes small-pox, as it occurs in man, sheep-pox or ovinia, and chicken-pox. The second group practically never occurs in epidemics, is due to an accidental or intentional inoculation, the virus from the eruption being definitely transmitted in a known manner into an abrasion of the skin, at which point it causes a local eruption, usually one or more pocks; and these diseases are rarely fatal. This group includes vaccinia or cowpox, horse-pox, and several other pock diseases, the nature of which is not very well understood, owing to the fact that opportunities for their study are rarely afforded. These include the pock disease of camels, of goats, and of monkeys; and it is quite probable that in all three of these instances we are dealing with one of the above diseases that has been inoculated into the animal in question.

Sheep-pox.—Sheep-pox occurs as an epidemic disease, the incubation of which is from eight to ten days. It is characterized by a general eruption and by constitutional symptoms, and it is attended by a very high mortality, from 25 to 50 per cent. If the virus from this disease is transmitted to healthy sheep by inoculation, a milder disease is produced, the incubation period of which varies from four to eight days, and when the sheep recover they are immune; but unfortunately this method of protection is attended with a too great mortality to be of any service.

Sheep-pox is not ordinarily a cause of death in man, and it is only with difficulty that it may be transferred to man by inoculation. When it had been transferred, as in the experiments of Sacco, it was found that it produced a local eruption which could not be told from ordinary vaccinia, and which afforded protection against small-pox. The difficulty of securing a successful inoculation and its tendency to spread in epidemics among sheep prevent its being used in producing immunity for small-pox in the human being. The disease may be transmitted to other animals, to cattle and to rabbits. If the virus from a vesicle in man, or from a cow, or from a rabbit, is reinoculated into healthy sheep, this retro-ovination is usually successful, produces only a local sore, and protects the sheep against sheep-pox. Sheep-pox may be transmitted to goats, and it is then usually called goat-pox. The virus obtained from goats has been used in the past to secure immunity against small-pox in man, but comparatively little is definitely known about this subject. The sheep is not ordinarily susceptible to human small-pox.

Horse-pox.—This is a local disease transmitted from one animal to another by inoculation. It is apt to occur as a local eruption about the fetlock joint of the hind legs, perhaps due to the frequent injury of this part of the body. Sometimes it produces a more or less widespread eruption from auto-inoculation; and a general eruption may be produced by injecting the virus into the veins or lymphatics of colts. The disease may be transmitted to cows, in which case it is usually carried by the milker, who has previously dressed the sores on the horse. Jenner thought that cowpox was derived from horse-pox, but this is questionable. Both human small-pox and cowpox, if inoculated into the horse, are capable of causing lesions which it is difficult or impossible to distinguish from the ordinary natural horse-pox. Inoculated into man, it produces vesicles that resemble the vesicles of vaccinia, and it protects from small-pox, as has been proved by the experiments of Sacco and also of Loy. The pock disease of camels mentioned above may be transmitted to man, usually accidentally, as on the hands of milkers; and individuals so affected are said to be protected from small-pox.

Ape-pox.—Monkeys are susceptible to small-pox, and during epidemics in the tropics they have been known to take the disease naturally. They may be vaccinated with cowpox, and an immunity produced in this way. When the small-pox lymph is inoculated into monkeys, it usually causes only a local sore, but sometimes this is accompanied by a general eruption.

Cowpox.—The most important of all the pock diseases of animals, however, is the cowpox or vaccinia. This is seen as a result of inoculation of the virus of the disease from one animal to another, and it occasionally occurs without any such apparent inoculation. This latter is designated as natural cowpox. Natural cowpox apparently never has been a very common disease, and it is much rarer now than formerly, so much so, indeed, that a single case of it is recorded in the literature and is regarded as a matter of great interest. It is a disease which is more apt to be seen in the spring or early summer, at the time when there is the greatest flow of milk, and it almost always affects cows, but it has been observed both in calves and in bulls. When it starts in a herd, it spreads rapidly, usually being transmitted by means of the hands of the milkers. The cow may have fever and loss of appetite before the appearance of the eruption on the skin, or the eruption may be the first thing noted. There is a slight difference between the eruption in the natural cowpox and the inoculated variety. In the former the eruption comes out in crops, so that the various stages of the eruption may be noted on the udders at the same time, just as in human chicken-pox the eruption comes out in successive crops. In the inoculated cowpox, however, all of the papules start at the same time and run through their course in about the same manner. The udder becomes swollen and painful, and there are small red papules present, which vary in size from ½ to 2 to 3 cm. Vesicles appear on these and they become multilocular. They may or may not be umbilicated. In about a week the clear lymph has changed to pus, and on about the twelfth day the eruption begins to dry up. During the pustular stage there are usually constitutional symptoms, chief of which is fever. There may be slight variations in the course of the disease, and considerable variation in the appearance of the eruption due to secondary infections, which sometimes produce marked ulceration. The scabs usually separate between the eighteenth and twenty-first day and leave behind typical scars. One attack confers immunity which apparently lasts as long as the cow lives. The immunity produced in man differs from this, in that it gradually becomes weaker and may wear off, so that the individual becomes susceptible to small-pox and also to cowpox; and a subsequent vaccination may produce a second sore and a second immunity. This varies considerably in different individuals.

Cowpox is easily transmitted to man, and when this is accidentally done the inoculation is usually upon the hands of those milking the cows. Inoculated into animals it produces a local sore. In passing through some animals it seems to gain in virulence, for example, in the rabbit, a lymph which in losing its virulence will usually regain it. In sheep, it produces a general eruption, and the disease may become highly contagious for other sheep and occur in epidemic form so that cowpox inoculation cannot be used to protect sheep from sheep-pox.

History of Vaccination

The history of vaccination dates back to the traditions that have been handed down in almost all countries, in various parts of Asia and Europe and in Mexico, that individuals who have been affected by cowpox or the other pock diseases of animals have been regarded as immune to small-pox. There are vague traditions that the disease has been purposely transmitted to man with the idea of producing immunity. Individuals having immunity to small-pox by reason of their having had an accidental inoculation have at various times been subjected to inoculations, the first of which is probably that of Sutton and Fewster, who, in England in 1788, inoculated such an individual with small-pox, the inoculation being unsuccessful. Heim relates that he was told by his father, in 1763, that individuals who had had cowpox were not susceptible to small-pox. Bose, in 1769, also noted this fact.

The first undoubted record of the cowpox virus being inoculated into man to prevent small-pox was the vaccination done in 1774 by Benjamin Jesty, a farmer living at Yetminster, in Dorset. He vaccinated his wife and two sons. Platt, a German school teacher living near Kiel, in 1791 vaccinated some individuals in a similar manner; and there were various other sporadic experiments which need not be noted.

To Jenner belongs the credit of having thoroughly studied the question of immunity as it relates to cowpox and small-pox; and of having collected and published data and the records of his experiments; so that, due to his publication, vaccination rapidly became a world-wide procedure. There were many other workers in the field, too numerous to mention; but one cannot pass over without noting the work of Sacco, the Italian observer, who, next to Jenner, did more to promote our knowledge of vaccination, and consequently its use, than any one else. There is some difference of opinion as to when Jenner started his observations upon cowpox, but it was probably not until about 1778 that his attention became especially turned to this subject.

Jenner was apprenticed at a very early age to Messrs. Ludloy, practitioners at Sudbury, near Bristol, and he remained with them six years. It was during this period, according to Baron, that the famous milkmaid incident occurred. A young countrywoman came to seek advice; and the subject of small-pox was mentioned in her presence. She is said to have observed, "I cannot take that disease, for I have had cowpox." In 1778 he inoculated a certain Mrs. H. with small-pox virus and this was unsuccessful, a result which he attributed to her having previously had cowpox. From that time on he studied all the cases that he could find. In 1780 there is a record of a conversation which he had with his friend Edward Gardner, in which he explained the subject of the protection afforded against small-pox. In 1788 he took a drawing of the hand of a milker with cowpox to London, where it was shown to various members of the profession. The subject of cowpox became more or less talked about, and was the subject of conversation and lectures; and various references occurred in the medical publications. Jenner collected 16 cases in which individuals who had had accidental inoculations with cowpox were subsequently inoculated with small-pox, and all unsuccessfully. In 1796 an opportunity was presented, owing to the development of a cowpox vesicle on the hand of a dairy maid, Sarah Nelmes by name; and, on May 14, Jenner vaccinated James Phipps, a healthy boy of eight years of age, using a method similar to that used in the inoculation of small-pox. The vaccination ran a typical course, and six weeks later Jenner inoculated him with small-pox, but without success. In 1769 or 1797 Jenner sent a manuscript containing the results of his work to a friend who was in close connection with the president of the Royal Society, but he received the friendly advice not to publish the paper in the Transactions for fear of injuring his reputation. He therefore resolved to publish the article himself, which he did in 1798 under the title of "An Inquiry into the Causes and Effects of Variola Vaccinæ, a Disease Discovered in Some of the Western Counties in England, Particularly Gloucestershire, and Known by the Name of Cowpox." The publication of this paper brought forth a host of unfavorable criticisms, the most important of which were those of Dr. Ingenhousz, who opposed Jenner's ideas. The opposition at this time to vaccination was marked, and Jenner's statements were the subject of considerable ridicule. In the meantime his vaccine lymph, which had been transmitted through some five generations, had been lost. He succeeded, however, in again obtaining the cowpox virus and vaccinated others with it. Some of the medical men and scientists were interested in proving or disproving Jenner's theory, among whom may be mentioned Pearson and Woodville, who inoculated over 160 individuals with cowpox. Over 60 of these were afterward inoculated with small-pox, but none took the infection. In March, 1799, Pearson sent a letter in which he inclosed an infected thread to some 200 practitioners with the request that they try its effects and report their results. He also sent the virus to Paris, Berlin, Vienna, Geneva, Hanover, and to Portugal. This is not the place to go into the details of the discussion which took place at that time. Suffice it to say that Jenner published, in 1799, "Further Observations on Variola Vaccinæ, or Cowpox," and, in 1800, "A Continuation of Facts and Observations Relating to Variola Vaccinæ," and, in 1801, "The Origin of Vaccine Inoculation." In 1799 a public vaccine institute was started by the friends of vaccination, and Pearson was placed in charge of this. A few years later, in 1803, a Royal Institute for the extermination of small-pox was founded, and Jenner was placed at the head of it, a position which he retained for many years. Both of these institutes did a great work in spreading the propaganda of the prevention of small-pox. There was always more or less opposition to vaccination in England, and this was based on various grounds, perhaps chiefly because it was an encroachment on the rights of the individual. There were also objections of a more political nature raised in England; and more particularly in other countries some of the opposition was placed on religious grounds. The danger of transmitting syphilis also furnished a fruitful source of objection which was eventually overcome by the use of virus obtained from animals. There were numerous attempts to secure a vaccination law, but the opponents always succeeded in preventing its passage; and, in spite of numerous severe epidemics, a law was not passed until 1867. In 1855 the General Board of Health sent to 542 authorities in various parts of the world and secured replies from all of them on the efficiency of vaccination and its possible dangers. The results of this investigation were published in 1857, in the *Blue Book on Vaccination,* which still remains one of the greatest monuments to Jenner, as well as one of the most complete collections of facts concerning vaccination that we have. The efficiency of the English law has been impaired by the introduction of the conscience clause, which allows a person to object if he has conscientious scruples against vaccination. The progress in Ireland and Scotland was also slow. A compulsory law was passed in Scotland in 1864.

The early history of vaccination in various countries forms an interesting chapter in the history of medicine, but we can only mention a very few facts in connection with it. Next to the work of Jenner is that of Luigi Sacco, of Milan, who became a great friend of Jenner and started a vaccine institute, and did much toward spreading the practice of vaccination. No law has ever been passed in Italy making vaccination compulsory, but it has been fairly generally practiced. Following out the suggestions of Galbiati and Feola, Negri succeeded in elaborating the method of using animal virus in 1849; and this method has very largely supplanted the use of human virus in most countries. It is very frequently referred to as the Neapolitan method.

In France the first vaccinations were done by Valentin and Desoteux, and this method of preventing small-pox was greatly spread by Aubert and Huisson. In 1805 Napoleon had those of his soldiers who had not had small-pox vaccinated; and in 1809 the first decree in favor of vaccination was issued. Vaccination was never very popular, however, and was only imperfectly done, although considerable interest from a scientific standpoint has always been manifest. The report of the Commission of Lyons in 1865 and the subsequent publications of Chauveau are among the best-known articles. France paid dearly for neglect of vaccination in the Franco-Prussian War as noted below under the heading of Germany.

Vaccination was introduced into Spain and Portugal about 1800 and has been practiced to a greater or less extent, although there are no compulsory laws dealing with the subject.

In Austria the subject was taken up by Ferro and spread particularly through the efforts of de Carro, who vaccinated large numbers of individuals and circulated pamphlets and vaccine lymph at his own expense.

In 1801 he secured official recognition for it, and the Imperial and Royal Institute for foundlings was made the Vaccine Institute.

In Switzerland it was introduced by Odier. Vaccination was introduced early into Russia and vaccine institutes were founded in the largest cities; and the better classes have always availed themselves of this means of protection. As a country, Russia is rather poorly vaccinated; perhaps less since the abolition of serfdom, as the care of the landlord has been removed from the very lowest classes.

Vaccination has been practiced in Holland and Belgium, although there is no special legislation on the subject. It was introduced into Sweden in 1801, and, shortly after, a compulsory law was passed. In Norway and Denmark special decrees in favor of vaccination were issued in 1810, and, while these did not make vaccination compulsory, the interest taken almost amounted to a law.

The most satisfactory and interesting results have been obtained in Germany. Vaccination was introduced into the various German states; and in 1802 there was a public vaccine institution started in Berlin and shortly after in other cities.

In Prussia there was no law until 1816, when a law requiring that school children be vaccinated was passed; a law similar to one that had been adopted in Austria.

The first satisfactory compulsory vaccination law was passed in Bavaria in 1807, due to the influence of Reiter. This provided that all infants be vaccinated in their first year of life. The enforcement of this law resulted in small-pox becoming exceedingly rare in Bavaria.

In 1870 one of the worst epidemics of small-pox of recent times started and spread throughout Europe, largely owing to the movements of troops. This epidemic did not cease until after 1873, when peace had again restored the normal quiet. The Germans were fairly well vaccinated, for, while there was no revaccination law, those entering the army were always vaccinated; while in France vaccination was very poorly practiced, and, as a result, there were not only more cases in the French army, but they were of a more malignant type; and the mortality was very much greater in France. The absolute mortality was fifty times greater than in Germany; and the ratio of deaths to the number of cases nearly twice as great. Shortly after the formation of the German Empire the German vaccination law was passed, in 1874. This law provides that all infants must be vaccinated during the first year of life unless the infant has had small-pox during that period. If, for any reason, vaccination should be regarded as a dangerous procedure, owing to the ill health of the infant, it must be vaccinated within one year after its recovery from any such condition. Revaccination must be practiced when the child is twelve years of age, if in a public school, unless it has had small-pox during the past five years. If this vaccination is not successful it must be repeated the next year. There are special vaccine physicians provided for, so that vaccination may be had without cost, and the law provides that the individual vaccinated must return not earlier than the sixth nor later than the eighth day to the physician who vaccinated him in order that the result may be determined. Records of all vaccinations and the results must be kept by the physicians doing the vaccinations, and sent to the authorities at stated intervals. In addition to this the parents or guardian must obtain certificates of vaccination for all children under their care, and these are to be furnished when demanded by the authorities. The German law has not been passed or enforced without a certain amount of opposition; but so far the opponents have always been outvoted in the Reichstag. As a result of this thorough vaccination, Germany has had no epidemic since 1875; and there have been scarcely any cases of small-pox in Germany except those cases which have been imported from neighboring countries where vaccination is not practiced to such an extent.

In America inoculation was practiced particularly in New England, and Dr. Benjamin Waterhouse, of Boston, was particularly active in the prevention of small-pox. It was very natural that he should become interested in vaccination. In 1799 he wrote an article which was published in the *Columbian Sentinel* of March 12 entitled "Something Curious in the Medical Line." In July, 1800, after having secured some virus from England, he vaccinated his son and subsequently a servant boy twelve years of age, and an infant, and its nurse. These individuals were exposed to small-pox and also inoculated, with negative results. President Jefferson had his family vaccinated with the virus, which he secured from Waterhouse. From this stock the District of Columbia and many states were supplied. The practice of vaccination in the United States varies greatly in the different states, and the compulsory laws that exist have usually been the result of an epidemic; as, for example, in the case of Baltimore, where it was not until there had been several thousand cases and a very large number of deaths that a compulsory vaccination law was finally passed, which provided for the vaccination of all individuals, although the only inspection provided under ordinary circumstances is to see that the children are vaccinated when they enter school.

Cultivation in Vitro.—Steinhardt and Lambert, using the Harrison method of cultivating tissue in vitro, have made studies in rabies, vaccinia, and syphilis. They showed that there was a definite multiplication of virus in tissue cultures when corneal tissue was used in the culture medium. The multiplication was exceedingly slow and they were able to carry the growth through three inoculations.

The Preparation of Vaccine Virus.—Vaccine virus may be obtained in several different ways. The older method was to use humanized virus; and the lymph was taken direct from the vaccine vesicle and transferred to the arm of the person about to be vaccinated. It was the simplicity of this method which permitted the rapid spread of vaccination at the time when it was first introduced. If it was desired to preserve the virus, this was done by drying it on threads, ivory, or bone points. In more recent times it has been drawn into capillary tubes or into small bulbs, usually with the admixture of equal parts of glycerin. The lymph should be taken preferably on the eighth day, although it may be taken a day earlier. It is not a good plan to use the lymph after it has become purulent. This method has practically fallen into disuse with the exception of a few individual practitioners who continue to use it; and a few countries, of which may be mentioned Mexico, where it is said the human lymph is still preferred. In Germany the law prohibits the use of any except animal lymph, but it is probable that in the other European countries more or less human lymph is used and marketed. In collecting the lymph from the vesicle, radiating scarifications should be made, and the lymph taken up on the end of a lancet or in capillary tubes or bulbs. Sometimes it is taken upon clean glass slides and allowed to dry between two pieces. The advocates of the humanized lymph argue that the virus is less apt to be contaminated with bacteria, that it is more certain to take, especially when transferred directly from arm to arm, and that it is less expensive. There are other advantages urged which need scarcely be mentioned. The objection to it are the possible dangers of transmitting syphilis and other diseases; and, while the transmission of syphilis is a real danger, the disease is probably not caused in this way as often as was thought, as the vaccination of an infant with hereditary syphilis often causes the syphilitic eruption to appear at the site of the vaccination. The fact that the transference may occur, however, is sufficient ground to exclude humanized lymph from ordinary use. The danger of the transmission of tuberculosis, leprosy, and other diseases is a negligible quantity. For the use of animal lymph we are indebted to the Italian observers. For the most part members of the bovine family are used, although other animals may at times be substituted, the rabbit having a number of advocates.

The technic of preparing the vaccine virus consists, first, in having the proper seed. There has been in the past more or less contention, particularly by the antivaccinationists, that the seed vaccine was not uniform, that there was a possibility of its being horse-pox instead of cowpox, and that it was also probable that small-pox inoculated into animals and transferred for several generations was used. This question is of comparatively little importance, as it has been definitely proved that the vaccine virus used at the present day is capable of conferring the immunity which is desired, and the remote origin of the various strains of vaccine virus is only of academic interest.

The method here described is that used in the National Vaccine and Antitoxin Institute of Washington, D. C., but practically the same technic is used by the various firms interested in the production of vaccine virus; and in the United States this is done under rules which have been formulated by the U. S. Public Health and Marine Hospital Service. The chief variations will be noted. Country-bred heifer calves of from six to ten weeks of age are chosen, the heifers being preferred because they are more cleanly; and the young calves because they are more susceptible to the vaccine, and because they are less likely to develop tuberculosis. The animals are placed in a quarantine stable, the temperature is taken night and morning, and they are carefully inspected each day by a competent veterinarian. This period of quarantine lasts for seven days, and the vaccination is usually made on the seventh day. Some producers of vaccine virus test the calves to be used with tuberculin, but this procedure is often not carried out, owing to the fact that tuberculosis rarely develops in calves as young as those used, and, if it should, it would be discovered at the postmortem examination which is held on every animal immediately after the vaccine pulp has been removed. The danger of transmitting tuberculosis from a calf by means of vaccine virus is so remote as not to need serious consideration. Each calf is given an identifying number which becomes the laboratory number of the vaccine obtained from it, and appears upon each separate package of vaccine; and under this number there is a permanent record of the history of the animal, the kind of seed used, and the notes of all the veterinary and laboratory observations made in connection with it. A record is also kept of when the virus is shipped and to whom. After the animals have passed quarantine they are at once prepared for inoculation by carefully shaving the hair from the entire surface of the abdomen and scrubbing the calf thoroughly with green soap. Some antiseptic solution is then applied, which is subsequently washed off with sterile water. The calf is taken to the operating room, which is built after the manner of a modern operating room, with walls and floors of concrete and the furniture of white metal and glass. The whole room is kept scrupulously clean, the walls and furniture frequently washed with bichlorid solution. The operators work in clean white suits and every precaution is taken to render the operation as aseptic as possible. The inoculations are carried out by making a long superficial incision down the whole length of the abdomen, with cross incisions of one inch. The seed vaccine is thoroughly rubbed into these and then the animal is removed to the incubating room, which is kept at a uniform temperature of 70° F., and is darkened by drawn shades. The animals are fed only with pasteurized milk and are kept as clean as possible. On the sixth day, which is somewhat earlier than the time used for taking human lymph, as the vesicle develops more rapidly in the calf than in man, the animal is again removed to the operating room and the pulp removed, with the same aseptic precautions as had been used in making the inoculations. The lymph and pulp are gathered together by lightly curetting the vaccinated surface. In former days the lymph only was used, but it was found that the pulp, which consists of the remaining portions of the vaccine vesicle, contained more of the active principle than did the lymph, and that both together could be used to great advantage. This is placed in sterile vessels and removed to the laboratory, where it is thoroughly mixed with a solution of 50 per cent glycerin and 50 per cent normal salt solution. The mixture is then placed in a refrigerator and allowed to remain there for three or four weeks. At the end of that time samples are taken, and plate cultures made and incubated, each plate representing the quantity used in one vaccine point. Lymphs at this period vary, some showing several hundred colonies of bacteria to the vaccination, and others showing many times that number. The results of this primary test are recorded, and if the bacterial count is low another count is made in a week's time. This is continued until the lymph does not show over fifteen or twenty colonies of foreign bacteria to the vaccination. Occasionally the lymph shows no foreign growth whatever, so that it may be put out within a short time, as early as six weeks, with none or almost no colonies of bacteria to the vaccination. When the count is sufficiently low, the different cultures of bacteria are examined microscopically and a portion of the lymph is inoculated into fermentation tubes. At the end of seventy-two hours 2 c.c. of the bouillon culture is withdrawn from the fermentation tube and injected subcutaneously into guinea pigs. The absence of gas or anaërobic growth in the fermentation tube at the end of seventy-two hours, negative results from the injected guinea pigs, and negative results from the microscopic examination are all necessary before the lymph is finally passed. Sometimes the lymph is discarded, owing to the presence of the colon bacillus or other gas-producing organism. In former years the calf was kept from eight to ten days after the lymph was taken, but in no instance did a calf develop tetanus. If the postmortem examination, which is made immediately after the vaccine pulp is taken, shows infected lymph-nodes or lesions of any of the organs, the lymph and pulp are rejected. Everything used about the inoculation is thoroughly sterilized with a sterilization which is sufficient to kill the tetanus organism. Everything that can be is sterilized in an autoclave. The ivory points are sterilized by means of fractional steaming. The finished points and tubes are subjected to examination by means of cultures, and it has been shown that there is no contamination in charging the points or in filling the tubes.

Just as human vaccine virus occasionally runs out without any apparent reason, it so happens that in the calf it will do the same, so that the vaccine seed is transferred to rabbits from time to time, and this procedure seems to increase its virulence.

The diluent for the virus varies in different makes, but almost all substances used for this purpose have been discarded in favor of 50 per cent glycerin, which has been shown not only not to interfere with the preservation of the virus, but to lessen the number of foreign bacteria, especially when kept in a cold place; and it also prevents the possibility of the growth of the tetanus bacillus. The virus so preserved will keep perfectly well if kept cold; the temperature preferred is below 0° C. rather than above. At –10° C. the virus is almost perfectly preserved, and the lowest temperature which is necessary to kill the virus has never been determined. It even withstands the low temperature produced by liquid air. The virus is affected by heat, and exposure to 60° C. is sufficient to kill it. Virus will rapidly deteriorate at room temperature, and a short exposure at 21° C. (70° F.) renders the virus useless.

The Florida State Board of Health issues the following instructions:

Vaccine should be kept on ice until used.

Vaccine not kept at a low temperature becomes inert and will not "take." Dr. Elgin found that: Vaccine kept at 140° F. five minutes was dead. Vaccine kept at 132° F. five minutes was weakened. Vaccine kept at 98° F. three to four days was dead. (This is body temperature and about the temperature at which the vaccine would be kept if carried in the pocket.) Vaccine kept at 70° F. one to three weeks was weakened but not dead. Vaccine kept at 50° F. three to six months was still active. (This is about refrigerator temperature.) Vaccine kept at 10° F. four years was still active. The lesson is: Keep vaccine in the refrigerator until used. Don't use vaccine that has not been kept at low temperature and expect to get "takes." A Committee of the Standard Methods of Preparing Small-Pox Vaccine of the American Public Health Association found that an acidity of from ½ to 1 per cent and an alkalinity of ¼ to 1 per cent are unimportant. The degree of dilution varies somewhat; ordinarily diluted in the proportion of 1 to 8 has been found to be a dilution which practically always takes if everything else is all right; and, while very great dilutions will sometimes take as a matter of experiment, they are not suitable for ordinary practical purposes. Lanolin has been suggested and is sometimes used in hot climates, but it is more difficult to get a uniform distribution of the pulp than from the use of glycerin. The test for the bacterial contamination and practically for the tetanus bacillus is not uniform, and there is still some question as to what should constitute a proper test for the detection of tetanus germs. As a matter of fact the tetanus bacilli have been discovered in vaccine virus with very great rarity, but two observers, as far as I know, having ever demonstrated them. Extensive studies have been made by the United States Public Health Service (Bulletin of the Public Health Service, 1915, p. 111), and the most careful researches fail to reveal any vaccine virus contaminated with the tetanus bacillus. The danger of tetanus from the vaccine virus issued from a laboratory using the methods customary in this country is so slight that it need not be considered. Various antiseptic solutions have been suggested, such as chloretone, sodium biborate, boracic acid, toluol, potassium cyanid, phenol, and chloroform vapor. The addition of 1 per cent phenol in glycerin has been suggested. It apparently does not interfere with the efficiency of the virus in the three months' period which is usually allotted. Fornet suggests that sterile vaccine virus may be produced by the use of ether. A virus so treated is bacteriologically sterile and at the same time remains active for weeks. Other methods have been at times suggested.

The one outlined above is satisfactory, and the only advantage of the others is the possibility that the lymph may be put out more quickly, but it seems quite probable that the addition of these antiseptics would eventually affect the virus rather markedly.

Rabbit Virus.—Various observers have suggested the rabbit as being an animal which will produce a very pure and active virus. A delicate haired rabbit is chosen, the hair clipped off of a large area on the side and abdomen, and then closely shaven and scarified. The virus is then rubbed on and the animal kept in a germ-free cage with a raised wire floor through which excretions may pass. The animal is given a thoroughly cleaned carrot each day and on the fourth day is killed by chloroform. The whole animal is wet with 5 per cent phenol and the inoculated area is covered with a piece of cotton wet with the same solution and this is allowed to remain three minutes. This is then washed with sterile water and the vaccine collected by curetting. With the rabbit virus there is little if any danger of infection from tuberculosis, syphilis, or foot and mouth disease. Rabbits are not included in Salmon's list of animals subject to foot and mouth disease, and rabbits exposed to the disease apparently did not contract it. The amount of pulp that can be collected from a single rabbit is comparatively small; about an average sufficient for one hundred and fifty vaccinations can be obtained.

Rabbit Testicle Method.—Noguchi has been able to produce a vaccine virus free from bacteria by growing the virus in the testicle of the rabbit. The virus is first treated with ether, after the method of Fornet, to free it from bacteria as far as possible. It is then injected into the testicle, the needle being turned in various directions in order to obtain a more or less uniform distribution. The virus increases in the testicle and reaches its maximum four or five days after the injection, then remains stationary until after the eighth day, when it begins to diminish, and at the end of five weeks it has practically disappeared. The testes are removed and ground with sterile salt solution or 60 per cent glycerin, and this is kept as a stock emulsion. It is necessary to pass the virus through several rabbits in order to bring about an adaptation to the testes, as the strength during the first transfer may be less than the original specimen from which the strain was derived. Subsequently the activity rises until it reaches its maximum point, at which it equals that of the skin strain. The changes in the testicle of the rabbit consist of a little exudation in the interstitial spaces during the first twenty-four hours. After forty-eight hours there is a considerable swelling and induration, and this increases rapidly and the testicle becomes edematous. On the fourth day the color has become purplish red, and here and there are irregular yellowish areas of different sizes. After six days the testicle becomes softer, and the edema and filtration begin to grow less. From this time there is a rapid decrease in the size, so that on the tenth day the testicle is of a somewhat smaller size than normal.

Technic.—The technic of vaccination is very simple. The first thing to be considered is the site of the vaccination. As a general rule, the left arm is chosen and inoculation made in the neighborhood of the insertion of the deltoid. Occasionally the right arm is preferred, as in left-handed individuals. In girls the leg is usually chosen in order to avoid the unsightly scar on the arm. Some physicians place the inoculation about midway between the knee and ankle on the outer side of the leg.

I prefer a few inches below the knee on the inside, where it gives rise to less discomfort, and where the vesicle is much less apt to be ruptured. The objection that has been urged to vaccination upon the legs is that, in infants, it is more difficult to keep clean, but with very little care this difficulty can be overcome in the better class of people.[1]

In America, as a rule, only one insertion is made; sometimes two, placed at least an inch apart; and some authorities advise as many as five placed in the position of the pips of the five-spot of ordinary playing cards with at least one inch of skin between. It is a good plan where possible to make the distance even greater than this, as, when they are placed too close together, the vesicles become large, and there is danger of their coalescing or of the intervening skin becoming ulcerated. The skin should be thoroughly cleansed. In people who are not accustomed to frequent bathing the skin should be scrubbed with soft soap and water; this should be followed by sponging with from 50 to 90 per cent alcohol for a minute, and this should be allowed to dry completely before the vaccination is done. Schamberg and Kolmer have suggested painting the vaccinated area with a 4 per cent alcoholic solution of picric acid. This should be done forty-eight hours after the insertion of the lymph and in no way affects the success of the vaccination, but it lessens the degree of subsequent local inflammatory reaction. The skin is brought on a stretch by using the left hand, and then scarified, and for this purpose various forms of instruments are used, and various forms of scarification recommended.

My own preference is that of a needle, preferably a sharp, straight Hagedorn surgical needle, which is easily kept sterile by inserting it into a cork and keeping it in a small bottle filled with alcohol.

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[1] This is not my experience.—Editor.

An ordinary lancet may be used, a dull-pointed needle or an ivory or bone point. Small linear cuts a quarter of an inch long are made, and these cuts extend just down to the corium. Care should be taken not to cut them too deep so as to avoid bleeding which may wash out the vaccine virus. If these small cuts are used, rubbing in of the virus must be most carefully done, as the area of absorption of it is comparatively small. Small cuts have the advantage of healing rapidly and of presenting less danger of secondary infections; and the disadvantage that with unskilled operators the vaccination may fail to take. Sometimes a small area of skin is scraped with the instrument removing the upper layers just down to the corium. This produces a red, moist surface on which there should be little or no bleeding. This method has the advantage that it is exceedingly easy to secure an effective inoculation, and has the disadvantage that it is more easily infected with extraneous organisms. More recently abrading the skin in a manner similar to the method used in von Pirquet's tuberculosis test has been advised. For this a small instrument not unlike a minute screwdriver is used, and a small circle of skin is denuded by a rotary motion. Another method is the intradermic injection of the lymph, which is done with a hypodermic syringe, the needle being introduced not through the skin but into it, and a small quantity of the lymph injected. Another method is to make cross cuts like the cross-hatching on a drawing, having the cuts about one-twelfth of an inch apart and four or five inches in each direction. This furnishes a fairly large surface for inoculation, and if carefully done heals promptly and leaves comparatively little surface for infection with other organisms. After the scarification is done, the vaccine lymph is thoroughly rubbed in, using the bone or ivory point or the needle which has been used in scarifying. This rubbing in of the virus is very important, and, with skilled vaccinators and good lymph, almost every vaccination in a primary subject will take; while with unskilled vaccinators there are usually many negative results, due generally to insufficient attention to the rubbing of the virus, sometimes to having the cuts too deep, causing hemorrhage which washes the virus out, and at other times to having the cuts or abrasions too superficial. As to the choice of lymph, my own preference is for vaccine points covered with glycerinated virus and protected by a thick covering of paraffin. If the so-called dry points are used the virus should first be moistened with a drop of sterile water. When it is thoroughly dry a small pad of sterile gauze should be applied and this should be retained by a few turns of an ordinary roller bandage, or it may be kept in place by an adhesive strip for twenty-four hours. The child should not be bathed for twenty-four hours after the vaccination. Great care should be taken to protect the vaccinated surface from dirty clothing and from infection by scratching or rubbing. When the vaccination begins to take, a properly applied shield may be used to considerable advantage. The shield should be deep enough not to touch the vaccine vesicle at any point and should be broad enough to come well beyond the line of inflammation, and should not press on the skin so as to interfere with the circulation.

A very good method in using a shield is to cut out a piece of gauze and put it beneath the edges of the shield so as to avoid the firm pressure on the skin.

A method of protecting the vaccine vesicle, which I have found to work better than anything else, is to apply an oblong piece of gauze folded some six times and retain this by a strip of adhesive plaster applied around the arm well above and well below the vaccination. If the vesicle is ruptured in any way this dressing prevents secondary infection from taking place. It is cheap, easily applied, easily removed, and may be easily changed when soiled. It should be remembered in using vaccination shields that they should be removed at least once a day and thoroughly cleansed by the use of boric acid solutions.

Clinical History of Vaccination.—After the insertion of the vaccine virus, if the wound is unirritated and not infected with extraneous organisms, it usually dries up within the first three days and shows the same appearance as would be noted from an ordinary abrasion of the same character. There may be a transient redness about the vaccination which lasts three or four hours and then disappears. On the third or fourth day the site of the vaccination becomes changed, and a small papule gradually appears. Sometimes this papule does not appear until the fifth or even the sixth day, or later. It is usually, although not always, surrounded by an areola, which is noted below. In the next five days the papule becomes changed into a vesicle so that, on the eighth day after the inoculation, the vaccination presents the appearance of a full, tense vesicle with a depressed center and a shining, mother-of-pearl appearance; and it is at this stage that the humanized lymph is secured by those who use it for further vaccinations. The vesicle is usually small at first, increases in size, and the center becomes depressed or umbilicated. The lymph, which is at first perfectly clear, becomes cloudier and cloudier, until about the tenth day, when it presents the appearance of pus. From then on it begins to dry, and, on the thirteenth or fourteenth day, presents a scab which is thick in the center, thin on the edges, and which comes away between the fourteenth and twentieth day, leaving a red scar which becomes white in the next few months. The appearance of the scar is rather typical, and has been described as having the appearance of having been cut out of the skin with a sharp die. The bottom of the scab is pitted or foveated.

The areola about the vaccination usually comes on about the fifth day, although it may appear earlier, or later. It generally increases until about the tenth day and then subsides, usually rather rapidly. It varies from ½ to 5 cm. in width, and there are variations in different individuals and also with different varieties of lymph, and with the different methods of preserving the same. There is sometimes involvement of the cellular tissue surrounding the vaccination, and there may be enlargement and tenderness of the lymph-nodes of the axilla. It is rather difficult to draw a hard and fast line between what might be termed the normal variations of the appearance of the vaccination and variations due to what might be regarded as complications. There are sometimes additional pocks, usually referred to as accessory or supernumerary pocks, which appear about the original vaccination. These are, as a rule, much smaller and are supposed to have resulted from accidental inoculation of imperceptible abrasions or to the transmission of the virus through the lymph channels. Sometimes these may develop on various parts of the body and result in a generalized vaccinia, which is described below. Some of these accessory pocks run the course of an ordinary vaccination, while others may not advance beyond the stage of a papule. The size of the vaccination varies from 1 cm. or less to 2 cm. Occasionally they may be much larger in size, the very large ones usually resulting from the coalescence of two or more vesicles. They may even attain the size of 10 cm. in diameter. The course and general effect of these large vaccinations are about the same as the smaller ones. The contents of the vesicle are also subject to suppuration, more particularly in anemic and run-down children, in whom the pus may be present early and the contents may be watery or at times hemorrhagic.

The course varies somewhat with the virulence of the virus and the amount which has been inserted; and there is some difference due to individual peculiarities; and the course is somewhat more rapid in warm weather than in cold. It is also more rapid in revaccinations.

There are curious variations in the late development of the pock, the vesicle sometimes being delayed for ten or fifteen days, and there are cases in which it does not form for as long as four weeks. This is most apt to happen with dry lymph. At times the vaccination may not develop at first, but, when a second vaccination is done a week or so later, and even as late as three weeks after the first, the first one may start up and run along the same course. Occasionally the vaccination may develop earlier and is referred to as a precocious vaccination. This is rather rare and usually does not vary more than twenty-four hours, so that the appearance usually seen on the eighth day will be present the seventh day. These precocious vaccinations should always be regarded with suspicion, as being due to other processes than that of the vaccine virus, and the source of the lymph should be carefully inquired into. There are variations in the involution due to many causes, to individual peculiarities, to variations in the lymph, to the methods used in vaccinating, and to the treatment of the vaccination itself. When the vaccination is done during the incubation period of some infectious disease, such as measles or scarlet fever, there may be marked variations in the course. There may also be variations, as noted below, due to injury in picking off the scab and other extraneous causes. As a general rule, vaccination is complete and the scab separated within three weeks. The constitutional symptoms of vaccination vary greatly. In children under six months of age there is usually little or no disturbance, and this is also largely true for children under a year of age; although in the second six months there are more apt to be some general symptoms than in the first. This may consist simply of restlessness, the child not being quite up to its normal condition, but very frequently there is fever, which usually comes on about the third day. It comes and goes, reaching its height about the eighth day, or sometimes on the tenth. The older the child the more liable it is to have constitutional symptoms; and adults a little more frequently than children. Sometimes there is loss of appetite and vomiting, and there may occasionally be diarrhea. Sleeplessness is often a prominent symptom, and in older children and adults chills and rigors may be noted. There may be skin rashes, which, as a rule, appear about the fourth or fifth day. These consist frequently of slight erythematous patches or an urticarial eruption. Not infrequently there is an erythematous rash more or less widely distributed which comes on about the tenth day and which has sometimes been called the roseola vaccinosa. This lasts from two to three days and then disappears. The course of the urticarial eruptions is quite variable. Sometimes they come and go, and may last only a few hours; or they may persist for some days. There is a leukocytosis which begins about the third day, increases to the height of the vaccination about the tenth day, and disappears rapidly as the temperature falls. A curious vaccination phenomenon was pointed out by Bryce, of Edinburgh, in 1802. This consists in the fact that, if a second vaccination is done not later than five days after the first, the second vaccination takes just as if it had been a primary one; and it will overtake the first one in its course, mature, and fade at the same time. This attracted considerable attention many years ago, but the practice of repeating the vaccination within the first five days has fallen into disuse.

Treatment of Ruptured and Infected Vaccinations.—A great many of the sore arms are caused by a lack of treatment after the vesicle has been ruptured by an injury. If the gauze dressing above alluded to has been used there will be little danger of the vesicle becoming infected with extraneous organisms, but if the wound comes in contact with a dirty sleeve or is scratched with dirty fingers it is almost certain to become infected and give more or less discomfort, even if the individual is not rendered ill. A certain number of other sore arms are due to vaccination shields being placed on too tightly or being allowed to press upon the vesicle. The shield should always be removed once a day or even oftener, if necessary, and washed with boric acid solution. If the vesicle ruptures it should be washed with a boric acid solution and a dry sterile gauze dressing applied, which can be kept from adhering by the use of a small amount of mild antiseptic ointment, such as boric acid solution. If the wound becomes infected it should be treated just like any other infected wound. For this purpose one of the most effective dressings is 25 per cent alcohol in which as much boric acid as will dissolve has been added. If the wound ulcerates and is slow in healing, a stimulating ointment may be applied, one containing 1 dram (4.00 gm.) of bismuth subnitrate and 1 dram (4.00 gm.) of liquid tar ointment to 1 ounce (32.00 gm.) of zinc oxid ointment will be found of great service for the milder cases, and the more severe ones may be painted with a solution of 10 to 20 gr. (0.65 gm. to 1.20 gm.) of zinc chlorid to the ounce (32.00 gm.) of water, and, if the granulations are very exuberant, they may be cauterized, preferably by the use of trichloracetic acid or a crystal of copper sulphate.[2]

Indications for Vaccination.—The German law given above furnishes a good guide. Briefly it may be stated that every infant should be vaccinated during the first year of its life unless there are special contraindications. The younger the infant the less constitutional disturbance will be noted. As a rule, as soon as the infant is gaining in weight and doing well, vaccination may be performed. Between the third and fifth month will usually be found the most suitable time. The vaccination should be repeated some time before puberty, and should be repeated some time after this; always when the individual has been exposed to small-pox or if an epidemic is prevailing. If vaccination is properly done and does not take, it does not harm the individual any; and if it does take it shows that his immunity had partially worn off. The contra-indications to vaccination are, first, to avoid vaccinating children who are ill with other diseases and those infants who are not gaining in weight, even though vaccination rarely causes any special disturbance in such infants. Care should be taken not to vaccinate any one during the incubation period of any of the exanthematous diseases. Nor should a child be vaccinated during the course of any of these fevers, so that it is a good plan not to vaccinate children living in houses in which there is a case of an infectious disease. After a child has been vaccinated care should be taken not to expose it to any infection. The child should not be vaccinated if there is an extensive eczema prevailing, nor if it is suffering with any skin disease accompanied with pus formation, such as furunculosis. It should not be vaccinated if there is a running ear or an abscess, or any suppurating open wound. Bleeders should either not be vaccinated, or, if so, it should be done with great care so as to avoid producing hemorrhage. Cases of leukemia and pernicious anemia should not be vaccinated, nor should any person suffering with a severe constitutional disease be vaccinated unless there is special danger of his developing small-pox, such as exposure to a case or a liability to be exposed during an epidemic.

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[2] For many years I have made it the rule to apply Lassar's paste upon the vaccinated arm as soon as the pustule begins to form. To this is added salicylic acid to form a 1 per cent ointment:

℞ Acidi salicylici, 1.00 gm.; zinci oxidi, amyli āā 10.00 gm.; petrolati, 80.00 gm.

The arm is douched with sterile lukewarm water twice a day, after which the ointment is applied on sterile absorbent cotton and held in place by a roller bandage. In infants smaller quantities of salicylic acid may be used; in older ones, larger. In doing this no infection occurs, the crust formation is hastened, and detached early, leaving a surface denuded, which heals easily and early. Since I have applied this dressing I have had very little trouble with vaccination. I never vaccinate upon the leg in infants and young children.—Editor.

Influence of Vaccination on the Exanthems.—The course of German measles and scarlet fever is not altered by vaccination. It is possible, though, under certain conditions, that chicken-pox may predispose to a general vaccinia. There are certain difficulties in distinguishing between a general vaccinia and chicken-pox, and the evidence on this point is more or less questionable.

Vaccination in Whooping-cough.—There has been, for many years, an impression that vaccination done early in the course of whooping-cough exerts a beneficial influence on the course of his disease. This method of treating whooping-cough has not been used very extensively, and yet, from time to time, favorable reports have been made, and, as it is a good thing for every one to be thoroughly vaccinated, there certainly could be no objection to a thorough trial. Mehnert, in South Africa, has reported that, in young infants, the effect was that, as soon as the vaccine pustule developed, the paroxysm of cough became less and disappeared completely in fifteen days at a maximum.

Vaccination Scars.—There is great variation in vaccination scars. The typical scar is a round or oval or somewhat elongated cicatrix with distinct margins. The base is pitted or foveated, and has the general appearance of having been cut out with a sharp die. Sometimes the appearance of the scar is changed by infection of the vaccination wound, or by ulceration of it, so that it may not be typical in its appearance. In some instances the vaccination scar is smooth and on a level with the surrounding skin, and with very small pits, or, in some instances, none at all. The cause of these small pits is a matter of question; some authorities think that they are due to the presence of hair follicles or sebaceous glands, while others believe that they are due to some specific histologic change in the skin at the time of the vaccination. Not all vaccination scars are pitted, although it is the rule. Some other scars, such as those following furunculosis, may present the same pitted appearance and should not be mistaken for vaccination scars. The appearance of the scar differs somewhat with the kind of virus used, and somewhat with the method of vaccination. When the vaccination is done in such a manner as not to disturb the corium, and this escapes injury during the development and course of the vaccination, no scar whatever may be left. The size of the vaccination scar varies. In the days when human lymph was used the average size was stated by de Cantelou to be from 6 to 9 mm. With the bovine virus and the present methods of vaccination, the scar is usually from 10 to 15 mm. in diameter. Sometimes it may be as small as 4, and at other times it may reach quite a large size. After revaccination the scar is smaller or there may be none; and sometimes white lines are seen even when the vaccination did not take, due to the scratches made at the time of the inoculation. Occasionally there will be slight discoloration of the skin at the site of the attempted vaccination, which may or may not persist. In negroes, and sometimes in other individuals, the scar may be elevated and there may be distinct formation of keloids.

The prognostic value of vaccination scars has been studied by Welch and Schamberg. They made careful observations of the scars of all individuals entering the Pennsylvania Municipal Hospital, and they were classified as good, fair, and poor. Under the first head were included all cases presenting typical vaccine scars. Under the second head were included all cases with scars having the same general characteristics but not as distinctly marked; and under the third head all other scars which were said to be due to vaccinations, but which did not resemble the vaccination scar, were included. In many of the cases where there were poor scars it is rather evident that the individual had never been successfully vaccinated. The percentage of deaths in those vaccinated in infancy who had good scars was 6.5; those with fair scars 12.21; and those with poor scars 22.64. Taking all of these together, but bearing in mind that this number undoubtedly includes a number of individuals who had never been successfully vaccinated, the percentage of deaths was 12.53, while the percentage of deaths in the same institution in unvaccinated cases was 41.82. There is some difference of opinion regarding the number of scars. The British Commission believe that the greater number of marks the greater protection is enjoyed by the vaccinated person in relation to small-pox. Welch and Schamberg believe that the quality of the vaccine scar is a far more reliable index of the degree of protection than is the quantity; and in their experience it seemed to make little difference whether there was a single scar or multiple scars, the protection being apparently about the same. One should bear in mind in this connection that the truth of the matter is probably this: that, where the multiple scars are the results of several inoculations at the same time, the protection afforded is about the same as that produced by one inoculation; but where the multiple scars represent revaccinations at suitable intervals the immunity afforded is greater than where only one vaccination was performed.

Revaccination.—After a person has been vaccinated in infancy the immunity may be perfect and may last a lifetime. In most instances, however, the immunity is either only partial or it wears off after a number of years have elapsed. The susceptibility to vaccination seems to be present in about 75 per cent of the cases vaccinated in infancy, and is noted chiefly at about puberty or in early adult life. We also know that, at the time of small-pox epidemics, many cases occur in persons who have been vaccinated in infancy and in whom the vaccination has not been repeated. There is no way, at the present time, of telling whether a person is immune or not except by repeating the vaccination. The following table by Welch and Schamberg is of interest in this connection:

Susceptibility to Vaccination *

Condition		Cases	Deaths	Per-centage of Deaths
Under one year	Unvaccinated	134	86	64.18
	Vaccinated	2	0	0.0
One to seven years	Unvaccinated	676	280	41.42
	Vaccinated in infancy, good scars	11	0	0.0
	“ “ “ fair “	11	1	9.09
	“ “ “ poor “	16	1	6.25
	Total number vaccinated	38	2	5.26
Seven to fourteen years	Unvaccinated	320	87	27.19
	Vaccinated in infancy, good scars	61	2	3.28
	“ “ “ fair “	24	2	8.33
	“ “ “ poor “	64	9	14.06
	Total number vaccinated	149	13	8.72
Fourteen years and upward	Unvaccinated	1,742	868	49.83
	Vaccinated in infancy, good scars	1,864	138	7.4
	“ “ “ fair “	894	114	12.75
	“ “ “ poor “	1,240	313	25.24
	Total number vaccinated	3,998	565	14.13

* From Welch and Schamberg, Acute Contagious Diseases, 1905, p. 46.

Every one should be revaccinated, and this should be repeated at intervals until the vaccination ceases to take. Revaccination should not, however, be done closer together than four weeks. The course of the vaccination done the second time varies. There may be only a small red papule, which disappears in a few days, leaving no scar; or there may be a somewhat larger papule surrounded by a very faint areola and followed by the development of a small vesicle. This dries, the scab quickly separates, and there is no scar; or, at other times, the above course may be noted but the vaccination is more decided and the scab more adherent; and when it separates it leaves a slight though usually distinct pitted scar. In other individuals the second vaccination may resemble the primary vaccination and leave just as distinct a scar. One should be careful not to confuse a spurious vaccination with a revaccination.

The question occasionally arises as to whether a person who has had small-pox should be vaccinated. Inasmuch as vaccination, if it does not take, does no harm, such an individual should be vaccinated if exposed to the disease. As a rule, one attack of small-pox confers a complete immunity, which lasts a lifetime, so that, in persons who have had small-pox recently, it will practically always, if not always, be found that the vaccination will not take. It occasionally happens, however, that if the small-pox has been in infancy, or many years have elapsed since the attack, the immunity may not be perfect. I have seen one or two instances of the most typical vaccination in individuals in whom there can be no doubt at all but that they had been through a severe attack of small-pox. The effect of revaccination is to lessen, and, in fact, to almost obliterate, small-pox, as in the German Empire, where revaccination has been practiced since 1875, there have been no epidemics since that time.

Insusceptibility.—This is rare and it is very probable that most of the cases of insusceptibility to vaccination are due to temporary disturbances in the individual or the supposed insusceptibility is due to the use of sterile lymph; probably in almost all cases the latter. It would seem, however, that, in some individuals, at times apparently insusceptible, it may take on a subsequent trial. I have vaccinated some children five or six times before succeeding in getting a successful take, and, in these instances, although the best possible obtainable virus was used, it had been improperly handled at some time and had lost its vitality. There is no reason, however, why a person should not at one time be susceptible and at another insusceptible, just as an individual may be exposed to small-pox and not take it and then take it on a subsequent exposure.

Immunity.—The immunity produced by vaccination varies somewhat with the individual. There may be a few individuals who are naturally immune, but these are rare and cannot be taken into account in considering the question of small-pox from a public health standpoint. Vaccination done in infancy will confer permanent immunity in a certain number of individuals, but in others the immunity becomes weaker as time goes on, so that, in later life, these individuals may take small-pox if exposed to it. If they do take the disease it will be lighter and the mortality very much less. There is no way of telling at the present time whether the immunity has worn off or not except by a repetition of the vaccination. Individuals who have been revaccinated at intervals until the vaccination done with active virus no longer takes can feel perfectly safe of their immunity. This has been thoroughly demonstrated in cases of physicians and others who may be constantly exposed to the disease. The question of the immunity produced in the children born of women recently vaccinated varies somewhat. Berkhardt vaccinated 28 pregnant women and 6 of their children were subsequently vaccinated, all unsuccessfully. Kelloch vaccinated 36 pregnant women; in 14 primiparæ the children were successfully vaccinated when the mother had been vaccinated before the seventh month, and in the cases in which the mother had been vaccinated after the seventh month the vaccination failed to take. It would seem to show that, in women with their first child, the vaccination done before the seventh month does not confer any immunity upon the infant. In multiparæ the immunity seems to be conferred on the child when the vaccination is done even as early as the fifth month. Small-pox may be transmitted to the fetus in utero as early as the eighth month, and such children acquire immunity.

The question of vaccination after the person has been exposed to small-pox has always been a matter of considerable interest. Hanna, from a study of the subject, concludes that vaccination done subsequently to infection with small-pox will take up to the date of the onset, that the individual is afforded protection from small-pox when the vaccination is done within three days (it might be safer to say two days) after infection takes place. If the individual is vaccinated for the first time during this period it may not afford protection, but the case will be a light one. He believes that the disease is somewhat mitigated even if the vaccination is done up to the onset, and possibly even later. Up to the onset of the disease the vaccination runs an independent course. After the onset of the disease the vaccination is, as a rule, not successful, and if it takes it runs an independent course.

Vaccination Complications and Accidents

This is a very large and vexatious subject that has been much discussed, especially by the antivaccinationists, and perhaps the most valuable contributions are mentioned in the Report of the British Royal Commission, 1889-1897. There has been, too, a great deal of discussion of these subjects by the profession, and even the most enthusiastic supporters of vaccination admit that its practice is attended with some disagreeable features; but it should be especially borne in mind that many of these are due to carelessness, sometimes on the part of the vaccinator, but more often on the part of the person vaccinated. Any other skin wound of the same extent carelessly treated would give approximately the same number of complications. This is a point entirely overlooked by most writers.

The vaccination complications have been variously classified, and, from an etiological standpoint, they may be grouped under the headings of those due to the vaccine virus, and for which vaccination per se may be held directly responsible. These changes are, first, the normal vaccination vesicle and the areola around it, and sometimes supernumerary pocks, which three things are not to be regarded, of course, as complications, but as the normal effects of the virus. At times there may be produced a generalized vaccinia, sometimes a profuse erythema, and at others a roseola. Less often there are lichen, miliaria, purpura, erythema multiforme, and urticaria. The second group comprises the definite infections, either local or constitutional. These are noted below, but it might be said in passing that the constitutional infections, if animal lymph is used, are largely mythical. If human lymph is employed syphilis is a real danger, though a very rare one. Septicemia may occasionally occur, just as from any skin wound becoming infected. The third group comprises certain skin diseases which may be associated with or follow vaccination, but which probably have very little if any relation to the vaccination. These vaccination complications may be grouped as follows:

Normal vaccine
  Erythematous dermatitis (areola).
  Accessory or supernumerary pocks.
Spurious vaccination.
Generalized vaccinia.
Generalized vaccinia from auto-inoculation.
Generalized hemorrhagic vaccinia.
Generalized gangrenous vaccinia.
Generalized vaccine erythema or roseola.
Vaccine lichen.
Vaccine miliaria.
Urticaria.
Erythema multiforme.
Purpura.
Tinea tonsurans.
Erysipelas.
Impetigo contagiosa.
Furunculosis.
Sore arm and ulcer.
Cellulitis and lymphatic involvement.
Hemorrhagic vesicle.
Phlebitis.
Local gangrene.
Tinea.

Constitutional Complications:
Syphilis.
Tuberculosis?
Leprosy?
Tetanus?
Septicemia.

Skin Diseases Sometimes Associated:
- Pemphigus or bullous eruptions.
- Eczema.
- Psoriasis.
- Lupus.

The dates at which the eruptions and complications may be looked for have been tabulated by Acland as follows:

1. During the first three days: erythema; urticaria; vesicular and bullous eruptions; invaccinated erysipelas.
2. After the third day and until the pock reaches maturity: urticaria; lichen; lichen urticatus; erythema multiforme; accidental erysipelas.
3. About the end of the first week, and generally after the maturation of the pocks: generalized vaccinia—(*a*) by auto-inoculation, (*b*) by general infection; impetigo; accidental erysipelas; vaccinal ulceration; glandular abscess; septic infections; gangrene.
4. After the involution of the pocks: invaccinated disease, for example, syphilis.

COMPLICATIONS DUE TO VACCINE VIRUS

Spurious Vaccination.—A curious phenomenon which occasionally is noted is the development of a red papule, usually between the third and seventh day after vaccination. This is at first a sort of raspberry color and crusts form over it, but no real vesicle; and this crust may at times separate or be pulled off accidentally or intentionally. After several weeks or even a month or more this disappears, leaving no scar. It is interesting to note that this was not described during the period in which humanized lymph alone was used. It has been noted by various authors since the general use of animal virus. This is not to be regarded in any sense as a vaccination and confers no protection.

Generalized Vaccinia.—Generalized vaccinia is met with now and then and seems to vary in its frequency in the experience of different observers. I have noted it quite a number of times, and I believe it is frequently overlooked or not reported to the physician. It is not transmitted from one individual to another except through inoculation, and in this respect differs from small-pox and from chicken-pox. It usually starts between the fourth and tenth day after vaccination, and the eruption comes out in crops so that all stages may be seen at one time. These crops may continue to come out for some days, and may even continue to appear for as long as four weeks, although this is unusual. The number of pocks varies greatly. Sometimes there are only three or four, and at other times they may be very numerous. They first appear as red spots, which change into shotlike papules, and these change into vesicles, and then to pustules, and then dry up. The vesicles are usually present from the third to the ninth day, the maximum development being about the ninth. They remain more or less stationary during the tenth and eleventh days, and then dry up and usually fall off on the sixteenth or seventeenth day. They may come on the mucous membranes, are apt to be noted in the mouth, and sometimes on the conjunctiva. In this latter situation they may cause considerable pain and be accompanied by a large amount of edema. The eruption in some respects looks like small-pox, and is sometimes mistaken for it, and sometimes for chicken-pox. It may be tested in case of extreme doubt by inoculating it into an animal. It is attended with general symptoms in some instances, and these may be severe but in many cases the indisposition is trifling.

The cause of generalized vaccinia is not entirely clear, but it is evidently due to the transmission of the virus either through the lymph channels or through the general circulation, and it has been observed more frequently when there is a general skin eruption, quite apart from any auto-inoculation. It may be produced by the admission of the virus through the digestive tract, through the circulation, or through the respiratory tract. It has been particularly noted in children who have sucked the pocks and so taken the virus into the digestive tract; among those who have noted this is Etienne. It has also been noted in a child sucking the breast of its mother who was undergoing vaccination. A generalized eruption has also been produced by the administration of the dried vaccine crusts with the food, as in the experiment of Cazalas. Sometimes it would seem that the lymph was the cause of the trouble, and there have been various epidemics reported, among which may be noted an epidemic in South Africa observed by Hill and Ross, in which the rash began between the eighth and fourteenth day and continued to come out for some five or six weeks. In this instance the lymph was obtained from one source only, and about three-fourths of the persons attacked were inoculated from a package bearing one number which apparently came from one particular calf, but the total amount of lymph was evidently taken from six different calves, which suggests a particular quality that was inherent in the strain of lymph and not in the reaction of any particular calf. Chauveau has reported general vaccinia in horses produced by the ingestion of the virus in the alimentary tract, by the respiratory tract, by the circulation, and also by injection subcutaneously.

Generalized Vaccinia from Auto-inoculation.—When an individual is suffering with any skin disease or has numerous abrasions upon the skin, and the vesicle upon the arm becomes ruptured, the virus is easily transferred from one part of the body to another, usually by scratching, and in some instances a very severe generalized vaccinia has been produced. Auto-inoculations are most common upon the cheek, upon the tongue, breasts, and buttocks, and are liable to affect patches of eczema, owing to the fact that the eczema itches and is scratched, but no part of the body is exempt. When inoculation occurs on the eyelid or on the eyeball, most serious lesions may result and even the sight of the eye itself be lost. There is an instance on record in which a physician vaccinated several children and was then asked by the mother to remove a foreign body from her eye. The physician did this, everting the lid without washing his hands. An accidental vaccination resulted, in which the eye was only saved by a continuous and careful treatment. Sometimes the virus is inoculated about the anus or the vulva, in which case the inoculations may be mistaken for chancroids or true chancre. The diagnosis is made chiefly upon the typical appearance of the vesicle and subsequently upon the course which it runs, and really should not present any great difficulties to any one familiar with the vaccine vesicle. It not infrequently happens, however, that such cases go for treatment to members of the profession who are not familiar, or only vaguely so, with the appearance of the vaccine vesicle, and mistakes have thus been made. The virus may not only be transferred directly from the vaccine wound, but various objects may be contaminated. Sponges, wash cloths, towels, handkerchiefs, beds, and baths have all served to transmit the virus, and even ointments that have been used on an open vaccine sore have transferred it. There is an instance on record of a gentleman who, being chafed from riding, applied vaselin from a jar that had been used to dress a vaccine sore. This resulted in a very extensive vaccination with marked constitutional disturbances. The only way to avoid these cases of auto-inoculation and accidental inoculation is the instruction of the vaccinated individual concerning the possible dangers. But, with the careless tendency of the average human being, it is not to be expected that they will not occur in the future, in spite of warnings.

Generalized Hemorrhagic Vaccinia.—This is a very rare occurrence, and is similar to the hemorrhagic eruption which apparently may occasionally be noted in any of the acute exanthemata. It varies in its intensity, the hemorrhage into the pock may be very marked or it may be very slight. In some cases not all of the vesicles are affected. At the same time there are apt to be petechiæ, subcutaneous ecchymoses, particularly upon slight bruising of the skin, and there may be hemorrhage from the mucous membranes and hematuria.

Generalized Gangrenous Vaccinia.—Under the heading of gangrenous vaccinia two conditions have been confused, one noted below, which consists of a local gangrene at the site of the vaccination, the other a generalized gangrene which starts as a generalized vaccinia and which becomes gangrenous, very similar to the gangrene which is occasionally noted in the course of chicken-pox. Not all of the pocks are affected. There may be only a few or there may be quite a number, and if those affected are situated close together the gangrene may extend from one to the other. The change usually begins at the latter part of the first week or the beginning of the second. At other times the papules instead of developing vesicles start to ulcerate, increase in size, then turn dark, and there is a sloughing of the central part. This may stop at any time and the patient may recover, or what is more liable to happen is that it may extend, the patient becomes cachectic, and eventually dies. This condition is not very well understood, and it is of such rare occurrence that very little opportunity has been given for the study of it by the more modern methods of investigation. Crocker believes that there is a dermatitis gangrenosa independent of the vaccinia which is possibly due to some pathogenic organism, possibly the Bacillus pyocyaneus. Others have believed that the condition was due to some alteration in the tissues due to syphilis, tuberculosis, rickets, or some other constitutional disease, and that changes have taken place in the skin which rendered it particularly liable to gangrene.

Generalized Vaccine Erythema.—Sometimes accompanying the vaccination there is a generalized erythema which may cover almost the entire body, or at other times may only affect portions of it. The eruption is a diffuse blush suggesting erysipelas, but nothing like as intense and usually without any constitutional symptoms. It varies in its appearance, and, at times, in place of being a diffuse erythema, occurs in small blotches, and at other times in small papules, suggesting measles. It usually comes out the ninth or tenth day, but it may appear as early as the third day or as late as the eighteenth after the vaccination. It usually lasts from a few hours to one or two days, and is of very little importance except perhaps from the standpoint of diagnosis. It is most apt to be confused with scarlet fever, with measles, or with erysipelas. The absence of the initial vomiting and high fever, and usually the absence of a sore-throat and always of the tongue signs of scarlet fever, should make the diagnosis comparatively easy. It should be remembered, too, that the eruption of scarlet fever consists of minute punctate spots, which, for the most part, are so close together that they give an appearance of a uniform blush. As a rule, the vaccinia erythema is merely a uniform blush without the punctate appearance. From measles the diagnosis is comparatively easy, owing to the absence of Koplik spots and of the involvement of the mucous membranes. From erysipelas the diagnosis is, as a rule, easy, because erysipelas is sharply outlined, more raised, and more painful, and accompanied by more fever.

Vaccinal Lichen.—This is a rather rare complication, so much so that one is almost inclined to believe that the cases reported are only accidental association of lichen and vaccination. The eruption has very much the appearance of the ordinary lichen, with perhaps a little more irregularity in its course. The eruption consists of small papules, which are red, somewhat conical in shape, and the size of a pin head. They are surrounded by a slight area of redness, and the edge of the papule has a polished appearance, so that it looks as though it had been rubbed over and a portion of it removed. The shape of the papule is not quite round and the outline more or less angular. Some of the papules are surmounted by minute vesicles and some of these change into minute pustules. It comes out in crops in about one-half the cases, is located on the vaccinated arm, and these are the cases which would seem to have some definite relation to the vaccination. The eruption usually makes its appearance on about the eighth day, but may be seen as early as the fourth day, or as late as the eighteenth.

Vaccinal Miliaria.—This is an eruption of small reddish papules, as a rule scattered over the body, and in many instances the papules are accompanied by small vesicles containing a watery fluid. These dry up after a few days and there may be slight desquamation over the affected areas. The eruption is apt to make its appearance between the eighth and twelfth days, and is not of frequent occurrence.

Urticaria.—This is one of the commonest of the skin eruptions accompanying vaccination, and is met with particularly in children who are known to be subject to this disease; but it may also be met with in children who have never been so affected. The eruption may make its appearance at any time after the vaccination is done, and consists of the typical wheals scattered over the body. Sometimes there are large diffuse areas of redness and sometimes a considerable amount of edema, particularly if the eruption is about the eye. Occasionally the eruption is bluish in color, is always accompanied by intense itching, and is usually characterized by rapid changes in its appearance and location, disappearing from one part of the body and coming out on another. It is frequently the source of further skin trouble due to scratching and infection of the scratch marks with pus germs. It can generally be more or less relieved by thorough powdering with talcum or starch powder, by the application of carbolized vaselin, and by sponging with hot bicarbonate of soda solution. Sometimes menthol solutions are applied, ½ to 1 per cent solutions in alcohol, painted over the surface, or the same strength used in an ointment. Internal administration of a brisk purge is often useful, as is also the use of some alkali, such as magnesia or bicarbonate of soda. Small doses of the aromatic spirits of ammonia are found particularly valuable. The urticaria may disappear promptly or may persist for days or even weeks.

Erythema Multiforme.—This is sometimes met with, and, in the lighter forms, merges clinically with the preceding, the urticaria often preceding an attack and the eruption changing to the typical appearance of erythema multiforme; and there is frequently the addition of purpura. The lesions may also be accompanied by slight swelling and pain in the joints. The lesions, all of which may be seen at the same time, may make their appearance any time between the first and tenth days or even later; and in parts of the body there may be diffuse redness and sometimes papules, sometimes vesicles and even pemphigoid eruptions. At other times the eruption consists of large, more or less round patches, varying in size and shape. These patches are not infrequently more or less cyanotic.

Purpura.—This may occur in connection with the above, or may be the only skin lesion present. It seems to be analogous to the hemorrhagic eruptions which are sometimes seen with the exanthematous diseases. It may or may not be accompanied by general symptoms. At times there is hemorrhages from the mucous membranes and hematuria, and there may be a slight swelling and pain in the joints.

Tinea Tonsurans.—This occasionally affects a vaccine sore, and it seems rather curious that it is not a more frequent complication. I do not know of any reported cases in America, but it has been noted on the continent of Europe, among others by Hagar and Eichstadt. It results from the transference of the fungus from an infected head to the vaccination, usually by scratching. There are certain forms of tinea met with in the calf, but these apparently have never been transmitted by vaccine virus.

Erysipelas.—This is due to the infection of the vaccination wound either at the time it is made or subsequently with the streptococcus which causes erysipelas. Considering the amount of neglect of vaccination wounds which exists, it seems strange that it is not a more common complication. Erysipelas is not an infrequent disease of infants and may develop quite independently of the vaccination. It has been stated that 2,000 per million infants under three months of age die from erysipelas. It is rather a serious disease when it develops, and when it occurs in infants may frequently prove fatal. The disease is caused by infection, either with unclean hands or instruments, or from lymph containing streptococci, or from unclean garments. Erysipelas following vaccination is much less frequent in recent years, owing to the fact that sterile instruments are more generally used and that the vaccine virus practically never contains streptococci, certainly not that used in America. With the proper protection of the vaccine wound erysipelas should almost entirely be done away with. The inflammation of the skin which is seen about the vaccination should not be mistaken for erysipelas.

Impetigo Contagiosa.—This is occasionally met with, particularly in children of the lower classes, and occasionally in infant asylums. It is most apt to occur in children who are living under bad hygienic surroundings and who are anemic or run down in health. The vaccination wound may be infected, or the impetigo may only occur on other parts of the body. It is easily inoculated from one part of the body to another and requires most careful technic to stop it when it is once started. The child suffering with impetigo, or who is exposed to it, should not be vaccinated except under very urgent necessity, such as having been directly exposed to small-pox.

Furunculosis.—This sometimes follows vaccination, and is particularly liable to develop in children who are run down in health, who are not well cared for, and who wear filthy clothing. It is particularly likely to be noted in epileptics and in the insane, especially those who do not keep themselves clean. The disease probably has very little connection with vaccination.

Sore Arm and Ulceration.—It is hard to draw the dividing line between the normal amount of inflammation in a vaccination and an abnormal amount. There is always more or less, as is demonstrated by the areola, which is part of the normal course of vaccination, and this varies in width and intensity in different individuals vaccinated in precisely the same manner. It not infrequently happens that it may extend for many inches away from the vaccination, and there may be considerable swelling. In a certain number of instances the inflammation is due to the infection of the vaccination with extraneous organisms, chiefly the streptococcus and staphylococcus. Infection may take place at the time the vaccination is done, or later, through a rupturing of the vesicle or pustule. Infection is more likely to occur in people with uncleanly habits, especially those who do not bathe frequently, and in whom the skin is liable to be the habitat of pus germs; but it not infrequently occurs from dirty finger nails scratching into the wound, or from coming in contact with filthy clothing. As a matter of fact it has always seemed strange to me that infection occurs as infrequently as it does. The inflammation varies greatly in its intensity. It may be more or less widespread and yet not very painful, and not attended with any great amount of discomfort; while at other times it may be intense, the arm swollen and painful, and the constitutional symptoms marked. The course of this infected vaccination varies so greatly that all phases of it cannot be described. Sometimes the tendency to ulceration is the most prominent feature. The ulcer may tend to spread, become large in size, discharge foul pus, slightly undermine the skin, and be very slow in healing and leave behind considerable scarring. At other times the process may be intense, but the healing may take place rather rapidly. In other instances there is not much tendency to ulcerate, although there is some; but the surrounding tissues are infiltrated, and a more or less widespread cellulitis results. Following this there may be phlebitis or sometimes lymphangitis, and the lymph-nodes in the axilla, which are almost invariably enlarged, may be the seat of suppuration.

Hemorrhage into the Pock.—It sometimes happens that, in place of the normal vesicle, there is a hemorrhagic effusion into it which may or may not be followed by ulceration.

Gangrene of the Pock.—This is not very common, but occasionally is noted following infection. For some reason or other the slough turns dark and a small area of gangrenous skin appears. This is followed by ulceration, the gangrenous portion usually separates, and healing usually takes place with considerable scarring.

Constitutional Complications and Skin Affections

Syphilis.—There are two things to be considered in connection with this: (1) the possibility of getting syphilis through vaccination; and (2) the effect of vaccination in syphilitics. The second point may be disposed of in a few words, as ordinarily the course of vaccination in a syphilitic individual is just the same as in the non-syphilitic. It occasionally happens that a baby, or even an adult, with active syphilis is vaccinated, in which case the syphilitic lesions may appear upon the vaccinated arm. As a general rule, vaccination should be avoided during the active symptoms of the disease unless there is extreme danger of small-pox. The question of the danger of getting syphilis from vaccination has been done away with since the introduction of bovine lymph, and, as this source of virus is used in most of the civilized countries, the question is almost of academic and historic interest only. But, inasmuch as arm-to-arm vaccination is occasionally still practiced, it may be well to call attention to the principal points concerning this subject, which has been discussed with unnecessary frequency in the past. There can be no question about the fact that, under certain circumstances, where arm-to-arm vaccination is practiced, syphilis may be transmitted. As a matter of actual fact, however, the number of cases of this disease from this source has always been few. Exceptionally the vaccination may be accidentally inoculated with syphilis, as might happen in the case of any open sore. Lee, in 30,000 children examined at the Great Ormond Street Hospital, in London, found only 1 case in which it was supposed that the vaccination may have been responsible for the syphilis. Inasmuch as the Great Ormond Street Hospital derives much of its clinical material from a population in which syphilis is not uncommon, it would seem almost strange that more cases of infection of vaccination sores have not been noted. Occasionally there have been epidemics observed, usually where a number of children were vaccinated from the arm of some one having the disease in a latent period. Almost the first, if not the very first, clear case is that reported by Marcolini in 1814. In this instance, from 1 girl 10 children were vaccinated, and from these some 30 more, and a number of these children developed syphilis. In another instance, reported by Tassani, 46 cases developed in 64 children and these infected several mothers and wet-nurses. Altogether there were 10 deaths, 8 of the children and 2 adults. Accounts of these epidemics might be multiplied greatly, but they all tell about the same story. Usually the syphilis was in a latent stage, and it is quite probable that a sufficient amount of care was not taken. In 1852 in Bavaria 8 out of 13 children developed the disease, and, from these, 9 other individuals were infected. In this particular instance the physician was condemned by the courts.

There was an opinion held for some time that the disease was transmitted only when the lymph was contaminated with blood, as it usually is in making arm-to-arm vaccinations. This was disproved by numerous experiments and it was found that the disease could undoubtedly be transmitted by clear lymph. In this connection mention should be made of the remarkable case of Dr. Cory, who vaccinated himself four times with the clear lymph taken from undoubted cases of syphilis. The first vaccination was successful; the second, done two years later, was negative; and the third, eighteen months later, was also negative. He then vaccinated himself in three places and developed syphilis from this last vaccination. This and other similar evidence disproved completely the theory alluded to above, which was advanced by Viennois, of Lyons, in 1860. In the transmission of the disease it makes no difference whether the vaccination takes or not. It does not necessarily follow that the disease is always transmitted when the lymph is taken from syphilitic subjects. As a matter of actual fact, the chances of not developing the disease are very good. Joukoffsky, in Petrograd, vaccinated 57 healthy children from the arms of 11 children who were subsequently found to be syphilitic. All of the 57 vaccinations took and in no instance did syphilis develop. The disease may not always be derived from the vaccine virus, but may be transmitted from an unclean lancet or by other means. Kussmaül relates an instance occurring in Lahr (Baden) in 1863 in which a number of children were infected with syphilis; the child from which the virus was derived was perfectly healthy, but the lancet used had previously been employed in opening an abscess of a syphilitic patient and had not been properly cleansed. The disease develops in from three to five weeks after the inoculation, but sometimes a greater period of time may elapse. The effects of the vaccination have usually passed, and on the site of the scar there develops a papule which ulcerates and presents the ordinary clinical picture of the hunterian chancre. About the only possibility of mistake in diagnosis is to mistake the chancre for an ordinary vaccination ulcer, or the reverse, mistaking the vaccination ulcer for the initial lesion of syphilis. There are certain differences which should render the diagnosis reasonably clear, especially to those familiar with the clinical history of both conditions. The incubation period of syphilis is usually three weeks or over, and never less than fifteen days; while the ulceration accompanying an ordinary vaccination develops between the twelfth and fifteenth days or even earlier. In syphilis the ulceration is only beginning, or even has not started, on the twenty-first day, while, in the ordinary ulceration, it is fully developed by the twenty-first day. If there are several vesicles, syphilis usually affects but one, while ulceration generally affects all. This is not always the case, and Hutchinson has reported an instance in which three chancres developed on the site of three vaccinations. The amount of inflammation present varies, but, as a rule, in syphilis it is slight, while in the ulceration it is usually very marked. The amount of tissue lost in syphilis is, as a rule, comparatively small, although occasionally the amount of it is marked. In the vaccinal ulceration the ulcer is almost always large and deep. The discharge of the chancre is small in amount or even absent and nearly always dries into scabs, while the discharge from the ulceration of a vaccination is considerable and it does not dry into scabs. The edges of the chancre do not present a punched-out appearance, but slope gradually to the bottom of the denuded surface, while in the ulceration there is the appearance as if the tissue had been cut out. The edges are perpendicular or even undermined, and the shape is irregular. The chancre presents a smooth, even appearance, while the ulcer has unhealthy granulations, often covered with pus. In syphilis the induration is circumscribed and has been described as being parchmentlike, and is easily outlined by palpation. The induration in the ulcer is irregular and apt to be extensive, and is not sharply outlined as a general rule. In syphilis there is no surrounding areola, or only a very small one, while in the ordinary ulceration the areola is very wide, and often presents almost the appearance of a beginning erysipelas. The lymph-nodes in syphilis are always enlarged, but they do not suppurate, while in the ulceration they may be enlarged and painful and have a distinct tendency to an acute inflammatory reaction. The eruption in syphilis develops late, usually several weeks after the appearance of the chancre, while the eruption in the ulceration comes on at the time of the vaccination, usually between the ninth and twelfth days. The eruption in syphilis is characteristic and almost always there are typical mucous patches on the mucous membranes. In the vaccinal ulceration the eruption is as described above under the heading of Vaccinal Eruptions.

Tuberculosis.—The danger of transmitting tuberculosis from vaccination is apparently purely imaginary. The lymph taken from calves is sure to be free from the tubercle bacilli, as tuberculosis is not apt to develop in calves as young as those used for the production of vaccine virus, and also because of the postmortem done on the calf immediately after the vaccine pulp is removed. The danger of tuberculosis when human lymph is used is apparently absent, as tubercle bacilli have never been found in vaccine lymph even in vaccinations on advanced cases of tuberculosis. Among other investigations along this line are the experiments of Jusserand, who injected the lymph taken from the vaccine vesicles in persons known to have tuberculosis into animals, and in no instance did any of the animals develop tuberculosis.

Lupus.—The question of lupus has also been raised. While there seems to be no doubt that cases of lupus have developed on the site of a previous vaccination, there is no evidence to show that this was not accidental, and the total number of cases reported is so small as to mean nothing in the vast number of vaccinations done.

Leprosy.—When animal lymph is used there can be no danger of the transmission of leprosy. It would seem that it might be possible to transmit the disease when lymph is taken from individuals suffering with leprosy, and there have been a few reports in which it was claimed that the disease was developed on the site of the previous inoculation. This subject has been given careful study by leprosy experts, among whom must be mentioned Hansen, of Bergen, who does not believe there is any danger of the transmission of the disease through vaccination.

Tetanus.—The development of tetanus after vaccination is rare, and, if the recent experience in the United States is omitted, it is practically unknown. The British Royal Vaccine Commission in 1896 reported only one case. There have been, curiously enough, in recent years in the United States, a number of small epidemics, most of which occurred in 1901. From a study of these cases, as far as it is possible from the reports, it would seem that the disease developed in the vaccine wound from a subsequent infection with the tetanus bacillus. In the first place, the tetanus bacillus does not develop either in the glycerinated virus or on dry points; and, in the second place, other children who were vaccinated with the same lymph as those who developed tetanus remained perfectly well. In most, if not all, instances there is a history of a wound of the vesicle. In some instances the scab had fallen on the ground and had been replaced; and, in other instances, the children played in stables or in gardens in which manure had been used, and, in one instance, a child slept in bed with its father, who was a hostler. Similar small epidemics of tetanus have frequently been reported quite apart from vaccination. The bacillus of tetanus has practically never been found in vaccine virus in spite of a considerable amount of research along this line.

Septicemia.—There is a certain amount of danger from blood poisoning, as when the vaccine wound is infected it presents the same possibility as is afforded by any other focus in which there are pus germs. Even epidemics of septicemia have been reported, but in every instance the lymph was from human source, and apparently considerable carelessness was used in handling it. Only one epidemic need be cited, and this is one which occurred in 1860 in Massachusetts. A number of children were vaccinated from a bottle containing a mixture of vaccine virus and snow water, which was used to dilute it. The first vaccinations took and ran a normal course. Subsequently, when this fluid in the bottle had decomposed, and had a definite odor, a number of other children were vaccinated and these developed abscesses and showed marked constitutional disturbances. In other instances the infection has come from clothes that have been washed in contaminated water. The methods of wound infection with pus organisms are so well known that further comment is unnecessary.

Pemphigus.—Curious eruptions of the skin have followed vaccination and some of these have the appearance of pemphigus. In some instances it would seem that there is an individual predisposition to have a bullous type, while in other cases it would seem that a certain strain of lymph is responsible for the lesion. Pernet has observed the fact that this form of disease is more frequent in butchers and those handling animal food products than in other individuals. It may be possible that there is some sensitizing of the tissues which renders the skin more susceptible than that of a normal individual. There have been instances in which there were epidemics, but the disease is not transmitted from one individual to another, and reinoculations of the lymph from the vesicles do not reproduce the disease; and the latter heal without a scar, so that this cannot be regarded as vaccination. Howe, of Boston, reported 10 cases, in all of which except 1 there was a history of a recent vaccination. The shortest incubation period was six days, the average five weeks, and the longest sixteen weeks. They all occurred in adults, and 6 of them proved fatal. Sometimes there is an eruption of the skin which looks like dermatitis herpetiformis, which comes on about one week after vaccination and sometimes as long as four weeks after, and it may persist for months.

Eczema.—It is not uncommon to see, in infants and in children with a tendency to eczema, an outbreak of this disease following vaccination. These outbreaks are so common in children with a tendency to eczema that it is not to be wondered at that a vaccination will sometimes start one. There is almost always a history of a family predisposition to eczema. As a general rule, with proper treatment, the attack is not to be feared, and it does not differ from those caused by other kinds of irritation.

Psoriasis.—It has been thought that this is due to vaccination in certain instances, but the evidence on which this opinion is based is very slight. There have been but very few cases reported, and it would seem that, if vaccination were a definite cause of psoriasis, considering the large number of vaccinations done, the disease would be more frequent. There are some fifteen cases in the literature which have been made much of by antivaccinationists and which may be regarded very much in the light of accidental association.

Drug Eruptions.—Care should be taken not to mistake eruptions caused by drugs for disturbances of the skin caused by vaccination. The eruptions from bromids, the iodids, arsenic, and belladonna are the ones most frequently met with, and could easily be mistaken for vaccine rashes. There are instances on record where the eruption caused by bromids and also by iodids has been mistaken for general vaccinia.

Value of Vaccination

It would seem hardly necessary to add a special section on the value of vaccination as a branch of preventive medicine, and yet, in spite of the experience of the past century, and the large quantities of well-known statistical material, there are many who refuse to be convinced that vaccination is the chief means which we have for preventing small-pox, and that it is responsible for the low death-rate from this disease in well-vaccinated countries.

There are a number of different ways of proving that vaccination is an effective preventive of small-pox, and among these is the direct inoculation test. This test cannot be made at the present time in most countries, owing to laws against inoculation, but there is sufficient evidence from tests made in the early years of vaccination to convince even the most skeptical.

Inoculation experiments were made by Jenner, who states that upward of 6,000 persons had been inoculated with the virus of cowpox, and the far greater part of these had been inoculated with the virus of small-pox and exposed to its infection in every rational way that could be desired, but without effect.

In America, among the various inoculation experiments, are those of Waterhouse and also those of Dr. James Smith, who was the attending physician to the County Almshouse in Baltimore, and who published in the *Telegraph,* one of the Baltimore daily papers, December 3 and 5, 1801, full accounts of the cases vaccinated by him in the Almshouse, all of whom were freely exposed to small-pox both by inoculation and in the natural way without any of them taking the disease. There are a large number of similar reports, all of which reach the same conclusion, and which therefore need not be quoted.

It should further be noted that the monkey reacts both to vaccination and to small-pox in the same manner as the human being, and that inoculation experiments have been made upon monkeys with the same results as those mentioned above. That is, that vaccination properly done furnishes a means of protection against small-pox.

A second form of evidence of the value of vaccination is the comparison between the prevalence of the disease before and after vaccination. Aitken states that from 1750 to 1800, according to the investigations of the Epidemiological Society of England, there were 96 deaths from small-pox out of every 1,000 deaths from all causes; while from 1800 to 1850 after the introduction of vaccination, but during the time in which there was no compulsory law, there were 35 deaths from small-pox out of every 1,000. In the various German states during the same periods there were 66.5 per 1,000 in the prevaccination period and 7.26 after the introduction of vaccination. It should be borne in mind that prior to the time of the introduction of vaccination small-pox was a disease of childhood, and that almost all the cases occurred before the seventh year. Haygarth states that about 1 person out of 20 escaped small-pox. After the introduction of vaccination the age at which the individuals were affected became changed, and now, when vaccination is practiced, it is more common to see cases in adult life than in children. A death from small-pox in a child under five, who has been successfully vaccinated, is a great rarity. In the prevaccination periods practically all the deaths, apart from epidemic years, occurred under ten years of age, and nine-tenths of these were under five years. This statement is not strictly true for all years, but will be found true for much of the period.

Some of the antivaccinationists state that the fall in the mortality rate from small-pox after the introduction of vaccination was due to the discontinuance of small-pox inoculations, but it should be borne in mind that the inoculated small-pox is much less fatal than that acquired naturally, and that individuals having inoculated small-pox must have contributed less to the fatal cases than those who derived it from natural contagion.

Inoculation was introduced into England in 1721, but was not practiced to any great extent until the latter half of the eighteenth century, and even then it never became general. If it caused any increase in the death-rate this increase should have come during the time inoculation was practiced, but, as a matter of fact, the mortality was as great before the introduction as it was afterward, and possibly greater. Inoculation was not practiced in Sweden, or at any rate very sparingly, and the influence of vaccination on the death-rate in Sweden was just as marked as in any other country.

Another claim of the opponents of vaccination is that small-pox is less frequent and less deadly owing to the fact that sanitation is better. This, however, is not the case, and we may cite the experience in Glasgow, in which town sanitation was probably worse during the first half of the nineteenth century than it was prior to that time. If we are to judge from certain reports on the sanitary condition of that city made between 1818 and 1838, we may be led to believe that the existing sanitary conditions were about as bad as could be found in any English town, and yet, notwithstanding this fact, the mortality from small-pox decreased nearly 80 per cent after the introduction of vaccination.

The third way of proving the value of vaccination is to cite the fact that, of the people who are properly vaccinated and who are exposed to the disease, few or none contract it. This is the universal experience in small-pox hospitals, where physicians and nurses are constantly subject to infection, and where it is a very exceptional thing for either to contract the disease.

During the epidemic in Philadelphia a number of workmen employed about the Municipal Hospital erecting additional buildings were so close to the patients that they were all advised to be vaccinated. There were between fifty and sixty men, and all except two complied with the request. The only ones to contract the disease were the two who were not vaccinated.

There have been frequent offers made to antivaccinationists to live in small-pox hospitals along with the same number of well-vaccinated physicians and nurses, and to compare the difference in susceptibility in the two classes of individuals, but up to the present time, so far as I know, no antivaccinationists have come forward to accept this method of proving their contention.

That vaccination lowered the death-rate and especially in early life is shown by the table giving the annual mortality per 1,000 inhabitants in Sweden. This includes, of course, deaths from all causes. It will be seen that not only is the total rate lowered, but the chief change is in those under five years.

ANNUAL MORTALITY TO 1,000 PERSONS LIVING—SWEDEN *

Ages	Before Vaccination		After Vaccination	
	21 Years (1755-1775)	20 Years (1776-1795)	20 Years (1821-1840)	10 Years (1841-1850)
Under 5 years	90.1	85.0	64.3	56.9
5 to 10 years	14.2	13.6	7.6	7.8
10 " 15 "	6.6	6.2	4.7	4.4
15 " 20 "	7.6	7.0	4.9	4.8
20 " 30 "	9.2	8.9	7.8	6.8
30 " 40 "	12.2	11.6	11.8	9.8
40 " 50 "	17.4	16.1	16.7	14.5
50 " 60 "	26.4	23.9	26.0	23.6
60 " 70 "	48.1	49.3	49.4	46.3
70 " 80 "	102.3	104.1	112.9	102.8
80 " 90 "	207.8	197.4	243.7	228.5
90 years and upward	394.1	351.3	396.4	375.8
All ages	28.9	26.8	23.3	20.5

* From Welch and Schamberg, Acute Contagious Diseases, 1905, 114.

Some idea of the death-rate from small-pox in prevaccination times can be gathered from a study of the table showing the deaths in Geneva over a period of one hundred and eighty years. It will be noted that the greater mortality is during the first year of life, and that nearly all the deaths occurred before the first ten years. The reason for this is that nearly every one had contracted the disease before ten and had either died or acquired an immunity, so that the number of adults affected with the disease was small and consequently there were but few deaths.

SMALL-POX DEATHS AT VARIOUS AGES, 25,349 CASES (GENEVA, 1580-1760) *

Number in Age Class	Years	Per Cent of the Total
6,792	0- 1	26.8
5,416	1- 2	21.4
4,116	2- 3	16.2
2,826	3- 4	11.1
1,928	4- 5	7.6
1,325	5- 6	5.2
944	6- 7	3.7
543	7- 8	2.5
454	8- 9	1.8
345	9-10	1.4
267	10-15	1.0
141	15-20	0.6
87	20-25	0.3
48	25-30	0.2
17 in age above	30	0.1

* From Allbutt and Rolleston, System of Medicine, 1909, ii. Part 1, 776.

The statistics from an epidemic in prevaccination times in Posen, 1795 to 1796, in the villages of Rawicz, Vojanowo, and Sarnowo, are of considerable interest. The population of these three villages was 13,329, and 1,252 contracted small-pox, or 9.4 per cent, of which 199, or 1.5 per cent, died; while 15.9 per cent of those who had small-pox died. The distribution by years was:

From 0- 5 years	743, or 59.3 per cent.
From 5-10 years	441, or 35.2 per cent.
From 0-10 years	1,184, or 94.8 per cent.
Over 10 years	68, or 5.2 per cent.

The prevalence of small-pox varied in various districts and from year to year, as statistics were not always kept in the most perfect manner; but, from the reports which may be regarded as the most reliable, we find that the death-rates were everywhere very high. For example, at Kilmarnock, 1728 to 1764, out of every 1,000 children born alive, 161 died of small-pox. In Berlin it was estimated that from one-twelfth to one-thirteenth of the deaths were due to this disease. At the present day, in countries where there is no vaccination, small-pox rages just as it did prior to vaccination time. In the Russian Empire, 1893 to 1898, it was stated that there were 275,502 deaths from small-pox. During the same period, in Spain, where the population was only ten and a half million people, there were 23,881 deaths. Throughout China and the East small-pox still continues to rage. Contrast Germany during the five years noted above for

Tables Comparing Small-pox Mortality in Various Localities before and after the Introduction of Vaccination *

Terms of Years Respecting Which Particulars are Given		Territory	Approximate Average Annual Death-rate by Small-pox per Million of Living Population	
Before Vaccination	After Vaccination		Before Introduction of Vaccination	After Introduction of Vaccination
1777-1806 and	1807-1850	Austria, Lower	2,484	340
1777-1806 “	1807-1850	Austria, Upper, and Salzburg	1,421	501
1777-1806 “	1807-1850	Styria	1,052	446
1777-1806 “	1807-1850	Illyria	518	244
1777-1806 “	1807-1850	Trieste	14,046	182
1777-1803 “	1807-1850	Tyrol and Vorarlberg	911	170
1777-1806 “	1807-1850	Bohemia	2,174	215
1777-1806 “	1807-1850	Moravia	5,402	255
1777-1806 “	1807-1850	Silesia (Austrian)	5,812	198
1777-1806 “	1807-1850	Galicia	1,194	676
1787-1806 “	1807-1850	Bukowina	3,527	516
	1817-1850	Dalmatia	....	86
	1817-1850	Lombardy	....	87
	1817-1850	Venice	....	70
	1831-1850	Military Frontier	....	288
1776-1780 “	1810-1850	Prussia (East Province)	3,321	556
1780 “	1810-1850	Prussia (West Province)	2,272	356
1780 “	1816-1850	Posen	1,911	743
1776-1780 “	1810-1850	Brandenburgh	2,181	181
1776-1780 “	1816-1850	Westphalia	2,643	114
1776-1780 “	1816-1850	Rhenish Provinces	908	90
1781-1805 “	1810-1850	Berlin	3,422	176
1776-1780 “	1816-1850	Saxony (Prussian)	719	170
1780 “	1810-1850	Pomerania	1,774	130
	1810-1850	Silesia (Prussian)	....	310
1774-1801 “	1810-1850	Sweden	2,050	158
1751-1800 “	1801-1850	Copenhagen	3,128	286

* From Welch and Schamberg, Acute Contagious Diseases, 1905, 108.

Russia and Spain and we find that there were only 287 deaths from small-pox. These figures could be multiplied almost indefinitely, all showing precisely the same thing.

The following table shows very well the difference in the deaths from small-pox before and after the introduction of vaccination, and it should be borne in mind that this table shows the results of vaccination carried out only partially and with practically no revaccination; and does not mean the results now obtained by the use of vaccination and revaccination, as it is done to-day in Germany, for example.

The same thing is shown in a somewhat different manner by contrasting the death-rate from small-pox in the vaccinated and the unvaccinated

DEATH-RATE OF SMALL-POX AMONG VACCINATED AND UNVACCINATED IN VARIOUS COUNTRIES *

Places and Times of Observation	Total Number of Cases Observed	Death-rate per 100 Cases	
		Among the Unvaccinated	Among the Vaccinated
France, 1816-1841	16,397	16⅛	1
Quebec, 1819-1820	?	27	1⅔
Philadelphia, 1825	140	60	0
Canton of Vaud, 1825-1829	5,838	24	2⅙
Darkehmen, 1828-1829	134	18⅘	0
Verona, 1828-1829	909	46⅔	5⅔
Milan, 1830-1851	10,240	38⅓	7⅔
Breslau, 1831-1833	220	53⅘	2⅑
Württemberg, 1831-1835	1,442	27⅓	7⅒
Carniola, 1834-1835	442	16¼	4⅖
Vienna Hospital, 1834	360	51¼	12½
Carinthia, 1834-1835	1,626	14½	½
Adriatic, 1835	1,002	15⅕	2⅘
Lower Austria, 1835	2,287	25⅘	11½
Bohemia, 1835-1855	15,640	29⅘	5⅙
Galicia, 1836	1,059	23½	5⅐
Dalmatia, 1836	723	19⅔	8¼
London Small-pox Hospital, 1836-1856	9,000	35	7
Vienna Hospital, 1837-1856	6,213	30	5
Kiel, 1852-1853	218	32	6
Württemberg, no date	6,258	38⁹⁄₁₀	3½
Malta, no date	7,570	21.07	4.2
Epidemiological Society Returns, no date	4,624	19.7	2.9

* From Welch and Schamberg, Acute Contagious Diseases, 1905, 117.

in various countries. The results always include among the vaccinated those persons who have been vaccinated, no matter what the result, and it is a notorious fact that many vaccinations done in countries where the laws are not strictly enforced are carelessly done, and give negative or imperfect results. But even with these unsuccessful vaccinations the results are remarkable.

The number of individuals attacked by small-pox will vary with the vaccination and the age. The most striking effect is seen in those under ten years of age, but it will be noted that the primary vaccination protects the individual over ten years to quite a considerable degree. Compare the table on page 230 with the German results of revaccination.

As noted under vaccination scars (which see) the protection will depend upon the thoroughness with which the vaccination is done—a lesson that may be learned by studying the vaccination marks, or, better, by the German methods and results. The following table shows very well the difference in the death-rate in those having good vaccination scars, those

SUSCEPTIBILITY OVER AND UNDER TEN YEARS OF AGE *

Place	Attack-rate under Ten		Attack-rate over Ten	
	Per Cent Vaccinated	Per Cent Unvaccinated	Per Cent Vaccinated	Per Cent Unvaccinated
Warrington	4.4	54.5	29.9	57.6
Dewsbury	10.2	50.8	27.7	53.4
Leicester	2.5	35.3	22.2	47.6
Gloucester	8.8	46.3	32.2	50.0

* From Allbutt and Rolleston, System of Medicine, 1909, ii, Part 1, 775.

having imperfect scars, which may be taken as more or less evidence of imperfect vaccination, and those having no scars.

DIFFERENCES IN DEATH-RATE AS EFFECTED BY VACCINATION *

Ages	Vaccinated Good Marks			Vaccinated Imperfect Marks			"Vaccinated," but No Evidence of Vaccination			Not Vaccinated		
Years	Cases	Deaths	Per Cent	Cases	Deaths	Per Cent	Cases	Deaths	Per Cent	Cases	Deaths	Per Cent
0- 2	4	0	0	32	3	9	22	9	41	276	181	66
2- 5	57	0	0	150	18	12	96	38	40	401	202	50
5-10	206	2	1	532	27	5	207	40	19	510	180	35
10-15	439	5	1	939	32	3	214	42	20	317	74	23
15-20	606	12	2	1,037	66	6	205	39	19	204	86	42
20-25	389	11	3	843	100	13	167	56	34	174	83	48
25-30	189	12	6	529	80	15	116	35	30	105	56	53
30-40	147	14	10	526	78	15	137	49	36	103	42	41
40-50	29	4	14	186	33	18	85	24	28	49	21	43
50 + ...	19	2	11	80	18	22½	46	20	43	30	13	43
All ages	2,085	62	3	4,854	455	9	1,295	352	27	2,169	938	43

* From Allbutt and Rolleston, System of Medicine, 1909, ii, Part 1, 785.

The decrease in the deaths from small-pox in England and Wales, where vaccination is not perfectly carried out, is well shown in the following table:

ANNUAL DEATH-RATES FROM SMALL-POX PER MILLION LIVING IN ENGLAND AND WALES, 1848-1903 *

Years	Under 5	5-10	10-15	15-25	25-45	45 and Upward
1848-1854	1,514	323	91	110	69	24
1855-1864	788.8	209.5	68.7	118.9	87.8	36.2
1865-1874	782.5	333.2	142.3	267.2	220.7	87.5
1875-1884	127.8	62.9	46.4	82.4	76.6	33.9
1885-1894	50.2	14.9	11.1	24.0	31.6	19.0
1895-1903†	31.2	12.6	7.3	10.1	20.9	17.5

* From Allbutt and Rolleston, System of Medicine, 1909, ii, Part 1, 772.
† Nine years.

The vaccination experience in Bohemia as outlined in the English Blue-book for seven years in the prevaccination period and twenty-four years after vaccination was introduced told the same story as the experience in other countries. The population of Bohemia during the first period was 3,039,722. There died annually 94,955, and there died annually from small-pox 7,663. After the introduction of vaccination, with an average population of 4,248,155, there died yearly 130,412, and there died yearly of small-pox 287.

Guttstadt states that in Berlin in the prevaccination period, from 1758 to 1802, the annual mortality from small-pox was over 8 per cent, with some bad years as follows:

	Per Cent
1766	22.1
1770	19.2
1786	21.2
1789	15
1801	21.2

After general vaccination in Berlin, the results between the years 1810 and 1814 showed an annual mortality from small-pox of 0.7 per cent, and from 1815 to 1869 the mortality varied from 0.06 per cent to 0.134 per cent, with an average of 0.8 per cent, or one-tenth of that in prevaccination times. From 1860 to 1870 there was a decrease in vaccination in Berlin, and in 1871 and 1872 the pandemic which swept over Europe affected Berlin very seriously. In 1871, 15.7 per cent died, and in 1872, 3.8 per cent. Comparing the prevaccination times up to 1870, the following tables from Immermann show the yearly average of people dying from small-pox per 100,000 inhabitants:[3]

1758-1762	407	persons	1790-1794	310	persons
1763-1767	364	"	1795-1799	239	"
1768-1772	294	"	1800-1804	261	"
1773-1784	(?)	"	1805-1809	306	"
1785-1789	360	"			
1810-1814	31	"	1840-1844	13	"
1815-1819	40	"	1845-1849	2	"
1820-1824	4	"	1850-1854	5	"
1825-1829	13	"	1855-1859	18	"
1830-1834	19	"	1860-1864	30	"
1835-1839	18	"	1865-1869	26	"

In 1870 to 1874 there was an average of 160 per 100,000 inhabitants a year, while from 1875 to 1884 the yearly average was only 1.16 per

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[3] From Nothnagel's Encyclopedia of Practical Medicine, American edition, 230, 1902.

100,000. This remarkable falling off is due to the vaccination law of 1874, which provided, as stated above, not only for vaccination, but for thorough revaccination. The results of this law are very well shown in the following table:

SMALL-POX DEATHS PER MILLION LIVING BEFORE THE GERMAN VACCINATION LAW OF 1874 *

Year	Prussia	Bavaria	Württemberg	German Empire †	Contrast Austria
1866	620	120	133	....	368
1867	432	250	63	....	484
1868	188	190	19	....	370
1869	194	101	74	....	374
1870	175	75	293	....	293
1871	2,432	1,045	1,130	....	383
1872	2,624	611	637	....	1,866
1873	356	176	30	....	3,094
1874	95	47	3	....	1,725

* From Welch and Schamberg, Acute Contagious Diseases, 1905, 124.
† No statistics.

SMALL-POX DEATHS PER MILLION LIVING SINCE THE GERMAN VACCINATION LAW OF 1874 *

Year	Prussia	Bavaria	Württemberg	German Empire †	Contrast Austria
1875	36	17	3	....	576
1876	31	13	1	....	406
1877	3.4	17	2	....	555
1878	7.1	13	0	....	631
1879	12.6	5	0	....	534
1880	26	12	5.6	....	674
1881	36.2	15	3.6	....	807
1882	36.4	12	6.6	....	947
1883	19.6	6	35.2	....	596
1884	14.4	1	11.6	....	530
1885	14	3	0	....	600
1886	4.9	1	1	4.2	400
1887	5	1.8	0	3.5	417
1888	2.9	3.8	0.5	2.3	615
1889	5.4	5.2	0	4.1	537
1890	1.2	1.5	0	1.2	249
1891	1.2	1.2	0	1.0	287
1892	3	0.5	0	2.1	256
1893	4.4	0.7	1	3.1	244
1894	2.5	0.3	0	1.7	105
1895	0.8	0.2	0	0.5	49
1896	0.2	0.2	0	0.2	36
1897	0.2	0	0	0.1	61
1898	0.4	0.3	0	0.3	....
1899	....	....	....	0.5	....

* From Welch and Schamberg, Acute Contagious Diseases, 1905, 124.
† No statistics.

In this connection it is interesting to note the effect of vaccination and revaccination in the German Army. It was introduced into Prussia in 1835. The preceding ten years, in a comparatively small army in Prussia at that time, there were 496 deaths. With the introduction of vaccination, the results are quite remarkable, as shown in the following table:[4]

1835-1844	altogether only	39 men
1845-1854	“ “	13 “
1855-1864	“ “	12 “
1865	“ “	1 “
1866	“ “	8 “
1867	“ “	2 “
1868	“ “	1 “
1869	“ “	1 “
1835-1869	altogether only	77 men

If one makes a comparison between the number of men dying in the army and the entire population of Prussia, one notes the most striking results in favor of the thoroughly vaccinated army.

NUMBER OF MEN DYING IN THE ARMY IN PROPORTION TO ENTIRE PRUSSIAN POPULATION *

	(A) Among the Entire Population of Prussia (according to official reports)	(B) In the Army (according to Prager)
1851	2.179 persons	3 men
1852	3.208 “	1 man
1853	6.734 “	1 “
1854	7.490 “	3 men
1855	1.664 “	0 “
1856	1.270 “	0 “
1857	2.330 “	1 man
1858	4.691 “	0 men
1859	3.530 “	2 “
1860	3.461 “	3 “

* From Nothnagel's Encyclopedia of Practical Medicine, American ed., 236, 1902.

The same thing could be shown by studying the effect of vaccination in other countries, but in no country has vaccination been as constantly carried out as in Germany.

In Chemnitz in Saxony there was an epidemic in 1870 and 1871 which was studied by Flinzer (Immermann). There were 64,222 inhabitants, and of these 53,891, or 83.9 per cent, were vaccinated. Five thousand seven hundred and twelve, or 8.9 per cent, had not been vaccinated, while

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[4] From Nothnagel's Encyclopedia of Practical Medicine, American ed., 230, 1902.

4,652, or 7.3 per cent, had already had small-pox. None of these last were affected by small-pox during the epidemic. There were 3,596 cases, or 5.6 per cent of the total population. Nine hundred and fifty-three were in vaccinated persons and 2,643 in unvaccinated; or, in other words, there was 1 case in every 56.7 of the vaccinated population, and 1 case in every 2.2 of the non-vaccinated. The relative mortality from small-pox for the vaccinated was twenty-six times less than for the non-vaccinated. There were 7 deaths among the vaccinated and 242 deaths among the non-vaccinated persons. In other words, in the vaccinated there was one death in every 7,698.7, while in the non-vaccinated there was 1 death in every 23.6, and a relative mortality of 326 to 1. Of the 935 vaccinated persons who had small-pox, 7 died, or 0.7 per cent, and of the 2,643 non-vaccinated persons 242 died, or 9.2 per cent, showing a mortality among the infected of almost thirteen times less in the vaccinated than in the non-vaccinated.

In Japan the history of vaccination is of considerable interest. According to Kitasato, small-pox was introduced into Japan in 123 B. C., at which time it caused a widespread and very fatal epidemic. From that time until 1868, when the present era began, there were some 50 epidemics, each one lasting several years and causing great suffering and many deaths. From 1875 to 1884 the number of patients suffering from small-pox averaged 208.1 per 100,000 of the population, while the deaths were only 494.6. There was a severe epidemic in 1885 lasting three years, a reappearance in 1892, when it again lasted three years, and a third outbreak lasting two years, beginning in 1896. In each one of these epidemics there were thousands of cases and thousands of deaths. A somewhat smaller epidemic occurred in 1907.

Vaccination was introduced into Japan in 1849 by a Dutch physician, Monicke, and vaccination stations were established in various cities. About this time, owing to political changes in Japan, all the modern features which had been previously introduced were forbidden, the only survivor being vaccination. The beginning of the first era in 1868 brought about many changes in the civilization of the East. The first vaccination law was passed in 1874, and this was revised in 1885, and more recently in 1909. The most recent law provides that each newborn baby shall be vaccinated within ninety days after birth and before June of the next year. Revaccination shall be made at the tenth year from birth. If either the primary or the secondary vaccination is unsuccessful, the child shall be revaccinated before December of the next year.

The difficulty in Japan has been to secure widespread successful vaccinations, but there is a great deal of small-pox both in China and Korea, and the disease is constantly being introduced into Japan so that in the past there have been epidemics from time to time. With each epidemic vaccination has been carried out, and the effect of vaccination in stopping epidemics has been very remarkable. It will be interesting to note the effects of the new vaccination law, provided it is carried out thoroughly, and doubtless the results will be the same as those in other countries which may adopt it.

Finally the experiences in Cuba and the Philippines show perhaps more conclusively than in other countries, with the exception of Germany, the value of vaccination in the prevention of small-pox.

Small-pox had been endemic throughout the island of Cuba for many years, and as there were no records kept during the Spanish administration there is no way of telling just how many people died, although one can get a fair idea from the mortality in Havana, where statistics are available for the past forty years. The number of deaths varied greatly, several years passing without any, or at other times there were over a thousand a year, and what might be regarded as the normal mortality from small-pox ran into the hundreds. Vaccination had been introduced into Cuba as early as 1804, but with a few exceptional years was never practiced extensively. In 1901 a commission was appointed to revise the vaccination law, and in the same year the new regulation was put into effect by the military governor of Cuba. The result of this was that by the end of the year 1901 Cuba was free from small-pox and the disease had not reappeared up to 1911. The vaccination law is sufficiently strict to result in vaccination in almost all, if not all, of the population, and although the island has been free from small-pox the practice of vaccination has been kept up, there being over 80,000 vaccinations reported in the year 1910.

In the Philippines the results have been just as striking. During the Spanish administration there were large numbers of cases of small-pox—so many, in fact, that large temporary hospitals were erected. Each year during the dry season the mortality was very high. It has been estimated that the annual mortality from small-pox was about 6,000 a year in the six provinces near Manila. Systematic vaccination was completed in 1907, and during the past five years there have been no deaths in Manila from small-pox, and the few scattered deaths which have occurred in the provinces have all been in persons not protected by vaccination. Similar conditions do not prevail all over the islands; for example, in the province of Cepu, prior to 1905, there were from 3,000 to 4,000 deaths each year from small-pox. In 1905 and 1906 there was a systematic vaccination of the 650,000 inhabitants, and in 1907 there were only 94 deaths. In the following two years the vaccination was not done as energetically, and in 1909 small-pox again became bad, and there were 736 deaths, over 90 per cent of which were in unvaccinated children. Vaccination was again renewed with increased vigor, and since that time small-pox has been practically absent. In the province of Bataan, in the town of Bagac, through a series of unfortunate circumstances, vaccination was suspended during a period of nine years. In 1905 there was a widespread epidemic; a thorough vaccination was done and within two weeks after it was completed new cases ceased to appear, and the town has remained free from small-pox since.

ANTIVACCINATION AGITATION

Councilman, in his article on small-pox, makes the statement that at the present time the disease is chiefly seen in the most ignorant and wretched population: the strollers who do not acquire a residence so as to be subject to vaccination laws, and the criminals who avoid the laws. The disease is also kept up by a class of people who are either ignorant or have a peculiar order of mind which renders them incapable of sane judgment, and who seek in every way to oppose vaccination. There are always certain members of every community whose minds seem to work in the opposite direction to those of most persons, and these individuals oppose almost everything on general principles. The amount of energy which they display in opposing any new thing and often old-established things is only equaled by the proselytes of a new faith or the propagandists of some new reform. Vaccination has been tested thoroughly in the crucible of doubt, and the result is that, while in the process some of the objectionable features of vaccination have been done away with, the fact as to its efficiency is unquestioned by any one who has made a careful and unprejudiced study of the subject. There can be no question of the fact that vaccination protects the individual from small-pox. The only question which is debatable is whether a compulsory vaccination law is proper from the standpoint that it interferes with the liberty and the personal rights of the individual. On the theory that the government must carry out those things which will work the greatest good for the greatest number, some of the more enlightened countries have insisted on thorough vaccination laws. Every unvaccinated person is likely to take small-pox, and every person with small-pox means a new focus of the disease from which it may spread. The objections which have been urged against vaccination are many, and they have not always been the same. Objections which were very potent many years ago have been entirely abandoned by the antivaccinationists of to-day. The chief objection, that of the possibility of acquiring syphilis, has been done away with through the use of bovine lymph. The danger of acquiring either tuberculosis or leprosy need scarcely be considered. In the early days people feared that in using a remedy which came from a cow there was danger of producing a bovinizing influence on the race and the cartoons of the period show the future generations with horns and hoofs. That there was nothing in this idea has been thoroughly proved by the lapse of time; and this feature is not mentioned by the opponents of vaccination. In earlier days, and even occasionally at the present day, antivaccination agitation is based on religious grounds. This does not carry much weight with it now, but there are still certain pious souls who regard disease as a scourge of God and that any means of combating it should be regarded as a sin. This same argument has been used against many other things.

The most powerful objection has come from the use of antivaccination agitation as a political weapon, and, while in the United States it has not been of much importance, in certain other countries it has been brought into play by unscrupulous politicians who thus secured the aid of an energetic band of workers and of an idea which in many cases was used to screen the real object of the campaign. It has been opposed, too, as mentioned above, as taking away the liberty and free will of the individual; but a man who would willfully start a new focus of small-pox certainly is as great a criminal as an individual who would willfully start a fire in some one else's property; and there is no feeling whatever on the part of the community when the rights and the liberty of the incendiary are interfered with. There is also an impression that vaccination increases the general mortality. This can be very easily disproved by the definite statistics of any country where they are sufficiently complete to be of any value. Thus, for example, in Sweden in the years from 1756 to 1775, that is, before the vaccination time, the yearly death-rate was 28.9 per 1,000 inhabitants; in the years 1776 to 1795 it was 26.8, while from 1821 to 1840 it was only 23.3, and from 1841 to 1850 only 20.5. The general mortality of Sweden has diminished one-third. In place of increasing the mortality rate, vaccination in reality lowers it because it removes one of the greatest causes of death. It has also been urged that it affected the mortality of the young. By comparing the actual death-rate in Sweden per 1,000 for the different ages, this will be seen to be untrue:

DEATH-RATE IN SWEDEN PER 1,000 *

Age	1776 to 1795	1841 to 1850
Between 0 and 5 years	85.0	56.9
" 5 " 10 "	13.6	7.8
" 10 " 15 "	6.2	4.4
" 15 " 20 "	7.0	4.8
" 20 " 30 "	8.9	6.8
" 30 " 40 "	11.6	9.8, etc.

* From Nothnagel's Encyclopedia of Practical Medicine, American ed., 274, 1902.

It has further been urged that vaccination increases the number of deaths from other diseases. This is not true, and scarcely needs any consideration whatever. It is extremely rare nowadays to find an antivaccinationist who has ever seen a very severe case of small-pox, and, as far as I know, no unvaccinated antivaccinationists have come forward to accept offers that have been made to live in a small-pox hospital along with an equal number of well-vaccinated physicians, so as to note the difference in the number who contract the disease and who die from it.

SUMMARY

1. Up to the time of Jenner small-pox was the most common and most deadly of all diseases.
2. Inoculation as a preventive measure was never very widely practiced, and was open to objections which do not apply to vaccination.
3. Vaccination, properly done, produces immunity to small-pox.
4. Vaccination properly done is practically free from danger.
5. With improved technic, the danger from syphilis has been done away with. There will always be some accidents connected with vaccination, just as with every other human procedure.
6. Immunity is not lasting. One vaccination done in infancy lowers the morbidity and the mortality, but, as the immunity may partially or completely wear off, revaccination should be practiced at intervals.
7. The individual should be revaccinated, either at the school age, or at puberty, or in early adult life; and subsequently from time to time; and always when a small-pox epidemic threatens, or when the individual has been exposed to small-pox.
8. Small-pox has not changed in its character; and in unvaccinated people is the same deadly disease that it was in prevaccination times. The eradication of small-pox, in so far as it has been accomplished, has been done through the effect of vaccination.
9. Antivaccination agitation, in the light of our present knowledge, is only an exhibition of a certain type of mind which refuses to accept facts and deductions. The fact that vaccination prevents small-pox, when properly performed, is beyond question.
10. Some better method of producing immunity to small-pox may be discovered in the future, but until that discovery is made we must rely on vaccination for the prevention of the disease.

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CHAPTER XII

SCARLET FEVER

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TREATMENT

The treatment of scarlet fever may be conveniently divided into: (1) preventive treatment; (2) treatment of the attack; (3) treatment of complications and sequels.

The study of treatment, however, cannot be profitably undertaken without some review of what is known of the cause and the method of the dissemination of the disease. Recent investigations point to a special type of the hemolytic streptococcus as the etiological cause of scarlet fever.

Cause.—Analogy to other infectious diseases of which the etiology is better known indicates beyond question that scarlet fever is produced only by the communication of infectious organisms from the sick to the well or by contact with carriers. Many earlier studies were made in the effort to discover the nature of the infectious agent, and microörganisms of different sorts were described, but no results of importance obtained. The first investigations of promise were those of Klein, who recovered from patients with scarlet fever a microörganism called by him the "Streptococcus scarlatinæ" and believed to be the cause of the disease. He found the same germ, too, in connection with the oft-quoted "Hendon Cow Disease," and considered that there was an intimate relationship between scarlet fever and the disease of the udder. Recently Tunicliffe and Bliss have shown that different strains of streptococcus hemolyticus isolated from a number of cases of scarlet fever belonged to a distinct biological group and were different from the streptococci isolated from other sources, such as erysipelas, mastoiditis, measles, influenza, diphtheria and the normal throat. These studies were made by means of opsonin and agglutinin tests. Tunicliffe also states that persons associated with scarlet fever patients may develop tonsillitis without an exanthem and harbor hemolytic streptococci which belong to the same biologic group as those isolated from typical cases of scarlet fever. Various investigators have maintained the etiological relationship of a coccus with scarlet fever. Class, for instance, found a diplococcus constantly present in the throat, the desquamating epithelium, and the blood, and Baginski and Sommerfeldt reported a streptococcus in the pharynx as also in the blood of fatal cases. Salge showed that agglutination of the scarlatinal streptococcus was produced by the blood of scarlet fever patients. This is confirmed by Moser and von Pirquet, but denied by others, such as Dopter, who failed to find any specific agglutinating power in the scarlatinal serum. Kolmer, also, found an agglutinative reaction with the streptococcus in only a small percentage of cases.

Certain investigators, among them Landsteiner and Levaditi, claim the transmissibility of the disease to the higher apes, but that the nature of the virus is still unknown. Dochez claims to have produced scarlet fever in guinea pigs. Certain "inclusion bodies" have been found by Döhle constantly present in the polymorphonuclear cells of the blood in cases of scarlet fever. This has been confirmed by Kretschmer, by Nicoll and Williams and by Farfel. Inclusion bodies have also been found in the cells of the lymphatic glands and elsewhere by Bernhardt and by Höfer. Their presence in the blood appears to be of diagnostic importance, but their nature and etiological significance are unknown. Macewen found these inclusion bodies in 96 of 100 cases of scarlet fever. They are also found occasionally in measles, in the acute stage of diphtheria, and they are plentiful in typhus, erysipelas and septic conditions. The presence of sepsis, especially when caused by the streptococcus, seems necessary for the production of inclusion bodies. Macewen has tried without success to produce inclusion bodies by the injection of streptococci and pneumôcocci into animals.

Dick and Dick recently published the results of some human inoculations with a hemolytic streptococcus culture isolated from the infected finger of a nurse who was taking care of cases of scarlet fever. They claim to have thus been able to reproduce the disease experimentally. The same authors have used the diluted filtrate (1 : 1,000) of a culture of the scarlatinal streptococcus, which apparently contains a soluble toxin, in testing out the susceptibility of individuals to scarlet fever. Zingher has been able to verify their observations with the intradermal test and has added a control with heated toxin as a part of the test. He has identified four reactions similar to those noted with the Schick test for diphtheria susceptibility: that is, positive, negative, negative-pseudo and positive-combined reactions. Dick and Dick have apparently been able to produce an active immunity by increasing doses of the toxin. Active immunization with the toxin has been carried out by Zingher on over 1,500 children. He also has noted the development of antitoxic immunity in the injected individuals. Finally, Dick and Dick have produced an antitoxic serum by injecting horses with the streptococcus toxic filtrate. Dochez has also produced an antitoxic serum in horses by injecting these animals in a special way with the sedimented streptococcus mass from a broth culture. Dochez states that the apparently specific streptococcus has been isolated from the local wound in wound scarlet, from the infected burn in burn scarlet, from the lochial discharge in puerperal scarlet, and from patients and contaminated milk in a milk epidemic of scarlet fever. The conception of scarlet fever according to these recent observations is that of a local disease of the nasopharyngeal mucous membrane, caused by certain specific strains of the hemolytic streptococcus. A soluble toxin is produced locally, which is absorbed into the system of the patient and gives rise to the rash and constitutional symptoms. The toxin produced by this streptococcus in vitro can be utilized as a skin test for the determination of susceptibility and immunity to scarlet fever and for the purpose of producing an active immunity against this disease. The antitoxic serum can be used like diphtheria antitoxin in the prophylaxis of exposed susceptible individuals and in the treatment of actual cases of scarlet fever. Certainly the outlook for accurate diagnosis, curative and preventive inoculation in the case of scarlet fever has been notably enlarged. These observations lead one to hope that we shall soon have the same control over scarlet fever as we have at the present time over diphtheria.

One of the most difficult facts to explain, if the streptococcus is assumed to be the etiological cause of the disease, is the permanent immunity produced by one attack of scarlet fever. Such an immunity does not follow an infection with any other strain of the streptococcus hemolyticus, which produces such a variety of pathological processes. If we consider, however, scarlet fever as a combined toxic and bacterial infection, in which the immunity to the disease is mostly of an antitoxic and not to any extent of an antibacterial character, we can correlate the above facts with the known permanent immunity following an attack of scarlet fever.

Infectious Principle.—The portions of the body which especially harbor the infectious organisms of scarlet fever are the nasopharyngeal cavities. For many years the desquamating epithelium has been regarded as an element of especial danger. More recent studies are largely in accord and compel us to suspect that the scales possess little, if any, infectious, power, except as they have been contaminated by the poison from other sources, especially the mucous secretions.

It seems quite certain that the bacteria causing scarlet fever are present in the mucous secretions from the nasopharnygeal cavities of patients and of carriers and in the pathological purulent discharges of complications occurring during the course and convalescence from scarlet fever, such as purulent ear and sinus discharges, pus from empyema discharges, etc. This view would appear to be proved with fair certainty by the experiment of Stickler, who injected hypodermically 10 children with mucus from the mouth and pharynx. All of these developed severe attacks of scarlet fever.

Method of Dissemination and Persistence of Virulence.—The tenacity of life of the germ appears to be variable, but certainly under some circumstances is very great. Murchison gives an instance of persistence of vitality for four months; Lommel for one hundred and thirty-three days; and Sannée for seventy-three days. Not only is the germ capable of living for a comparatively long time apart from the body of the host, but it is often difficult to kill, as shown by its persistence in rooms in spite of the disinfecting methods which may have been employed. It is questionable whether the air carries the dry germs in a virulent form to any extent. Close contact with the patient is undoubtedly the most frequent way in which the disease is acquired, but it also seems certain that it is more easily transmitted mediately than, for instance, is measles. The bed and body clothing are ready carriers of the germs, as are books, toys, letters, and the like. The transmission by a third unaffected person is possible, but not common, if any degree of caution is preserved.

The possibility of the dissemination of scarlet fever by milk is a matter of great importance. Well-authenticated instances have repeatedly been reported where the disease has existed in the families of the milkers and was carried to others. This condition has been studied of recent years especially by Freeman and by Kober.

A very important means for the ready dissemination of the disease is by those who are just beginning to show symptoms, by those who are convalescent from it, and by those who probably have the disease in an unrecognized form.

Period of Greatest Infectiousness.—It appears certain that scarlet fever can be communicated at the very beginning of symptoms, and probably during the last few days of incubation. This belief in the early transmissibility of infection is the view adopted by many recent investigators. There are sufficient instances to prove that the infectiousness is great, if not greatest, early in the attack, or even just before symptoms appear. On the other hand, the fact that the disease may spread to other members of the family after an inmate of a scarlet fever hospital has returned home proves that the later periods of the disease are not without danger. The statistics of the English hospitals show the occurrence of "return cases" in about 3 or 4 per cent. The sentiment in many hospitals, however, as shown by Millard in twenty-one institutions, is that this occurrence is no more frequent after four weeks of illness, even if the patients are sent home still desquamating, than if the usual six weeks of isolation is adhered to. It is to be remembered, too, that transmission late in the attack by no means proves that the infection is produced in the later stages of the disease. It seems very probable that the return cases acquire the disease from patients with uncured affections of the nose and nasopharynx (Barlow, Preisich). It is likely that patients suffering from nasopharyngeal discharge or from purulent otitis, or purulent secretion from other sources consecutive to scarlet fever, may retain the power of communicating the disease for long periods, but that those without these affections are free from danger to others in from three to four weeks. The uncertainty in this matter is shown by the fact that Igl would make the exclusion from school only three weeks, while Schick advises from eight to nine weeks' absence; and Sörensen says that even this period does not insure safety.

Mode of Entrance of the Germ.—This is as yet not certainly known. The germs in the air close to the patient probably enter the nose and mouth of the exposed individual, and thence spread through the system by way of the bronchi and lungs, or are swallowed and enter through the alimentary tract. With the great susceptibility of the tonsils to the entrance of micro-organisms of other sorts, it is very likely that they play no inconspicuous part in scarlet fever. In the case of infection by milk, entrance of the germs may possibly be either by way of the tonsils or of the gastro-enteric tract; in surgical scarlet fever they probably enter through a wound already present.

Diagnosis.—Scarlet fever has to be distinguished from various eruptive diseases, such as measles and German measles, from septic rashes and from a variety of drug and serum rashes. Among the drug rashes those due to salicylates, belladonna and quinin are especially apt to be confusing.

Recently Schultz and Charlton described an intradermal test which they claim is of value in the diagnosis of scarlet fever. They observed, in treating cases of scarlet fever with convalescent serum, that on the day following the injection of the serum the rash had faded around the point of injection. They also found that the serum from normal individuals produced this fading of the rash. Neuman confirmed these results and in addition found that rashes from other causes, which resemble scarlet fever, were not extinguished by convalescent or normal serum. He also observed that the serums from cases of diphtheria, measles and other exanthemata reacted in the same way as normal serum. The serum from scarlet fever cases, however, during the first four days of the disease, did not produce the blanching. Schultz in a more recent publication states that blanching occurred in 100 per cent of the cases when the injections were made on the second day of the rash, and in 78 per cent of the cases injected on the third day of the rash. Tron confirms the results of previous investigators in that serum from scarlet fever patients during the first four days of the disease does not produce blanching.

Mair thinks it likely that the Schultz-Charlton reaction is a toxin-antitoxin phenomenon. The rash and other changes in the skin are due to a scarlatinal toxin, which affects the cells of the capillary walls, resulting in the erythema and exudative phenomena of scarlet fever. The serum injected, when it gives a positive reaction, is supposed to contain an antitoxin which is able to dislodge and neutralize the toxin fixed in the cells and so to restore their normal function in the area affected. Mair considers that the serum of normal individuals who give a positive Schultz-Charlton reaction contains the antitoxin and probably results from contact infection with the virus of scarlet fever. This would be analogous to the diphtheria antitoxin found in "naturally" immune individuals, which is probably produced as a result of repeated contact exposure to infection with the Klebs-Loeffler bacillus. This was shown quite definitely by Zingher in connection with the Schick-testing of over 350,000 school children in the public schools of New York City.

Most observers have noted that the serum of many normal individuals would blanch a fresh scarlet fever rash, but that in a certain percentage the blood-serum did not have this blanching power. The correct explanation is now quite clear for these observations. The blood-sera of individuals who have antitoxin in their blood and give a negative Dick skin test show a positive blanching phenomenon. On the other hand, the sera of individuals who have no antitoxin and show a positive Dick skin test do not have the power to cause a blanching in a fresh scarlet fever rash. The sera of the first group also have the property of neutralizing the scarlatinal streptococcus toxin, while the sera of the second group lack this property.

The test is made either with unheated serum or with serum heated to 56° for an hour. The unheated serum serves the purpose perfectly well. From 0.5 to 1 c.c. of the serum is injected intracutaneously into scarlet fever patients during the first four days of the eruption. Injections are made into the anterior pectoral region, the lower chest region, abdominal wall or thigh. The blanching of the rash in scarlet fever, that follows the intracutaneous injection of serum from normal negative Dick persons or convalescents from scarlet fever, is usually quite definite and involves on an average an irregular circular area of about 2.5 to 5 cm. in diameter. When the blanching is definite, it persists until the general rash fades, but in some cases it is only slightly perceptible and soon disappears entirely.

The Schultz-Charlton phenomenon is a rather crude test and of diagnostic importance only in the more pronounced types of scarlatinal rashes. It must be considered, however, of value as a diagnostic aid in many doubtful cases. In conjunction with the Dick test it will help in bringing light into the symptom complex known as scarlet fever, which no doubt includes at the present time a number of different clinical entities.

Preventive Treatment

In the light of the newer studies of scarlet fever it is evident that preventive treatment, to be really successful, should be carried out along the lines so accurately studied in connection with problems of diphtheria. In addition to the general measures described below we shall have to consider the Dick test as an important means for the selection of susceptible individuals, the use of scarlatinal antitoxic serum for passive immunization and of the streptococcus toxin for active immunization.

The Dick Test.—Among the new measures that give promise to revolutionize our accepted ideas of many phases of scarlet fever is the Dick test for the determination of susceptibility and immunity to scarlet fever. This corresponds very closely in many of its features to the well-known Schick test, which is used for determining susceptibility and immunity to diphtheria. Dick and Dick reported in the February 17, 1924, number of the *Journal of the American Medical Association* the results of a series of skin tests on 153 individuals. A soluble substance obtained in the filtrate from cultures of the scarlatinal type of the hemolytic streptococcus was injected intracutaneously. Positive reactions were indicated by a light redness of the skin from 2 to 3 cm. in diameter, with some swelling and occasionally slight tenderness. The reaction occurs in persons who have not had scarlet fever, also in scarlet fever patients during the early stages of the disease. As the disease progresses the reaction becomes less pronounced and is absent after recovery. This would seem to suggest the production of a neutralizing antitoxic substance as recovery from the disease takes place. This reaction is neutralized by mixing convalescent scarlatinal serum with the filtrate of the culture of streptococcus hemolyticus.

There are four different reactions that can be distinguished with the Dick test and these reactions correspond closely to the similar four reactions that are noted with the Schick test. There is a *positive,* a *negative,* a *pseudo* and a *combined* reaction.

To make the readings of the Dick reaction more accurate and avoid the confusion that is very likely to arise between positive and pseudoreactions, Zingher strongly recommends the use of a control test with toxin *which has been heated in its final dilution, in a water bath at boiling temperature for one hour.*

The toxin that gives rise to the positive reaction is destroyed by the heat, while the reacting proteins that cause the pseudoreaction are not affected. A control consisting of toxin neutralized by convalescent or negative Dick serum is not so good. Zingher has found that not only is the toxin neutralized but in many individuals the local action of the streptococcus protein is also neutralized, so that many pseudo and combined reactions appear as positive reactions. The control test with heated toxin is closely analogous to the one recommended by Zingher for use in the Schick test and serves the same purpose.

The final dilution (1:1,000) of the scarlet fever streptococcus toxin is more stable than the final dilution of diphtheria toxin for the Schick test. The final dilution can therefore be kept and used for several weeks without noticing any appreciable diminution in toxic strength.

Zingher has made studies with the Dick test among normal individuals along lines similar to those carried out with the Schick test. He investigated the susceptibility by age groups from birth to adult life and found it to correspond closely to the susceptibility to diphtheria as shown by the Schick test in different age groups. Table 1 shows the susceptibility by

TABLE 1

THE DICK TEST AT DIFFERENT AGE GROUPS (ZINGHER)

Age	Total Tested	Dick Positive	Dick Negative	Per Cent Dick Positive
0- 6 months	24	11	13	45.08
6-12 months	42	27	15	64.3
1- 2 years	89	62	27	70.0
2- 3 years	86	61	25	71.0
3- 4 years	87	49	38	56.3
4- 5 years	129	60	69	46.5
5-10 years	665	250	415	37.6
10-15 years	1,064	244	820	30.0
15-20 years	197	49	148	24.8
20 years up	117	21	96	18.0
Total	2,500	834	1,666	33.3

THE DICK TEST ON NURSES AT ST. VINCENT'S HOSPITAL

19-27 years	80	42	38	52.5

age groups of 2,500 individuals from different walks in life. It also shows the high proportion of susceptible individuals among nurses, similar to their high susceptibility to diphtheria, as shown by the Schick test. The fact that many nurses come into training schools from small communities where there has been little contact exposure to infection explains this.

Even by social groups Zingher has found a close analogy with the Schick test. Table 2, showing the results in two private schools, indicates this.

TABLE 2

THE DICK TEST AT HORACE MANN SCHOOL AND AT RIVERDALE COUNTRY SCHOOL, NEW YORK CITY (ZINGHER)

Age	Total Tested	Dick Positive	Dick Negative	Per Cent Dick Positive
6- 7 years	22	19	3	86.3
7- 8 years	15	11	4	73.3
8- 9 years	20	17	3	85.0
9-10 years	13	11	2	84.6
10-11 years	26	25	1	96.1
11-12 years	17	14	3	82.3
12-13 years	26	21	5	80.7
13-14 years	21	16	5	76.2
14-15 years	26	19	7	73.0
15-16 years	15	11	4	73.3
16-17 years	30	23	7	76.6
17-18 years	19	16	3	84.2
Total	250	203	47	81.2

Zingher has also made comparative studies with the reaction on mothers and their offspring. The results indicate that the reactions are similar in the mother and offspring during the first six months of life. The antibodies are transmitted through the placenta and persist in most infants for a period of about from six to nine months.

The blood-sera of individuals who give positive or negative Dick reactions were studied by Zingher for their properties in causing the extinction test of Schultz-Charlton in a fresh scarlet fever rash; also for their power to neutralize the toxic test fluid for the Dick reaction. The blood-serum of a person giving a "negative" or a "pseudo" Dick reaction causes blanching of the rash and neutralizes the test toxin.

The Dick test is positive as a rule during the first two days of scarlet fever, but becomes less strongly positive toward the end of seven days and negative towards the end of from ten to fifteen days, when the antitoxic properties begin to appear in the patient's serum. This can be shown by its power to blanch the scarlet fever rash and neutralize the Dick test toxin.

Table 3 shows results with the Dick test observed by Zingher in a group of scarlet fever cases during the early stages of the disease and during convalescence. He has applied the test to over 150 cases of scarlet fever during the first four days of the disease and found them to be positive in all but 3. In these 3 cases the diagnosis of scarlet fever was very doubtful. As the patients progressed into convalescence they showed a negative or a pseudoreaction.

TABLE 3

THE DICK TEST IN SCARLET FEVER CASES (ZINGHER)

Patient	Age in Years	Date of Admission	Number Days Ill on Admission	1st Dick Test		2d Dick Test		3d Dick Test		4th Dick Test	
				Days of Illness	Test	Days of Illness	Test	Days of Illness	Test	Days of Illness	Test
1—B.M. . .	6	4/ 5/24	2	2	+ +	7	+	22	—	30	—
2—G.T. . .	5	3/21/24	2	2	+	12	—	16	—	26	—
3—A.D. . .	7	4/15/24	2	3	±	6	—	12	—	20	—
4—G.B. . .	12	4/17/24	2	4	+	10	±	18	—		
5—M.W. . .	1.5	3/19/24	1	1	+ +	9	—	22	—	37	—
6—T.R. . .	21	2/26/24	2	2	+	5	—	10	—	26	—
7—D.G. . .	14	4/ 9/24	4	4	±	5	+	20	—	28	—
8—J.O.D.	6	4/24/24	2	2	—	3	—	11	—		
9—T.L. . .	4.5	4/ 6/24	3	3	+ +	7	+ +	22	+ +	30	+ +
10—V.B. . .	10	4/23/24	(10)	(11)	+ +	(12)	+ +	5	±	10	—
11—M.F. . .	40	4/ 5/24	2	2	+	7	+	22	+		

REMARKS

In No. 6 the cervical glands enlarged on twentieth day of illness. Enlargement of cervical glands in presence of antitoxic antibodies in circulation indicates that little if any antibacterial immunity has developed during convalescence.

In No. 8 the injection of 40 c.c. of Dochez serum on admission inhibited the Dick test.

No. 9 probably had no scarlet fever. There was no desquamation. Blood showed negative Schultz-Charlton test and no neutralization of scarlet fever toxin. That this patient did not develop scarlet fever after admission to the hospital is illustrative of a fact well recognized in diphtheria. Positive Schick reactors may be exposed to diphtheria and become carriers of the Klebs-Loeffler bacilli, yet they will not develop clinical diphtheria until the local resistance of the mucous membrane is destroyed by an inflammatory process or by an operation on tonsils, etc.

No. 10 developed scarlet fever five days after admission to hospital. Dick test made on eleventh and twelfth days indicated that child had had no scarlet fever before exposure. The Dick test was negative 15 days after admission to hospital and 10 days after attack of scarlet fever.

No. 11 shows that persistent positive Dick test even in convalescence from attack of scarlet fever may have to be changed. It is conceivable, however, that the different strains of hemolytic streptococci associated with scarlet fever may produce two or more different toxins, and therefore different antitoxic antibodies, which would not be indicated by the skin test performed with a single toxin.

A small proportion of the cases continues to show a positive Dick reaction throughout convalescence. While most of these patients have not desquamated, yet some do show desquamation. The question arises whether we are dealing with different toxins produced by different strains of the hemolytic streptococcus in scarlet fever, which give rise to different antitoxins. In view of the fact, however, that most of the patients with Scarlet Fever who desquamate during convalescence show a negative Dick test, we can assume that a single toxin is produced by the different agglutinative strains of the scarlatinal hemolytic streptococcus. The few patients who desquamated and yet gave a positive Dick test may not have been true cases of Scarlet Fever. Desquamation is known to occur in conjunction with the eruptive diseases and is not absolutely diagnostic of Scarlet Fever. On the other hand, absence of desquamation may go very well together with different clinical infections, which are due to a specific toxin producing hemolytic streptococcus, and yet show no eruption during the course of the disease. A recent report by Dabney on a series of acute mastoid infections occurring among the nurses of a contagious disease hospital tends to prove this; the presence of the specific scarlatinal organism in non-scarlatinal throat cultures as well as in cultures from a wound and from a case of osteomyelitis, as shown by Williams and by Zingher, is also strong evidence in this direction.

Zingher has also made quantitative studies with increasing concentrations of the test fluid to determine the approximate amount of antibodies that develop during the convalescence from scarlet fever, the antibody content of the serum of normal negative Dick reactors and of the antitoxic horse serum prepared by Dochez. The antibody content is determined by one of two methods: (1) by testing the individual directly with increasing concentrations of the test toxin, beginning as Dick recommended with a dilution of 1: 1,000 or indirectly; (2) by diluting equal volumes of the test toxin (1: 500) with increasing dilutions of the serum, adding it undiluted, 50, 33, 25, 20, 10, 5, 2.5 and 1 per cent, allowing the two mixtures to remain preferably at room temperature for thirty minutes and then injecting either all of these test mixtures or alternating ones into an individual who has shown a good positive reaction with the 1: 1,000 dilution. If the standard toxin dilution is 1 :1,000, then the serum is added to a toxin dilution of 1:500, so that the ultimate dilution of the toxin in the mixture is 1 :1,000. Another Dick test is made at the same time to serve for purposes of comparison. A measure of the antibody content will give valuable data in showing the suitability of donors of blood-serum for prophylaxis and for treatment. Normal or "naturally" immune donors can thus become available for this purpose. Another very important result of our ability to measure the antibody content of a serum is that it will enable us to determine one of the important characteristics of extracellular toxins, which is so well recognized in the case of diphtheria toxin, that is, the property of a toxin to be neutralized in multiple proportions by an antitoxic serum.

TABLE 4

Results with the Dick Test at Public School No. 4, Bronx (Zingher)

Age	Non-Immunes			Immunes			Total Tested	
	Positive	Combined	Total	Negative	Pseudo	Total	Number	Per Cent Positive
5- 6 yrs.	14	1	15	6	3	9	24	62.50
6- 7 yrs.	18	1	19	15	3	18	37	51.35
7- 8 yrs.	11	3	14	18	10	28	42	33.33
8- 9 yrs.	16	8	24	24	20	44	68	35.29
9-10 yrs.	6	6	12	31	17	48	60	20.00
10-15 yrs.	20	26	46	175	137	312	358	12.85
Total...	85	45	130	269	190	459	589	22.07

Schick Tests for Diphtheria Susceptibility or Immunity at Public School No. 4, Bronx

Total	Schick Positive	Per Cent Schick Positive
1,153	248	21.6

Table 4 shows the results obtained by Zingher with the Dick test in one of the public schools of New York City. It is interesting to note that the percentage of positive reactors by age groups corresponds closely to the percentage noted for the same age groups with the Schick test. The total percentage of positive Dick reactions in this school approached closely to the percentage of positive Schick reactions. In a comparison of the two reactions in the same children, he noted that in 10 per cent the Dick and Schick reactions were positive, in 58.3 per cent the two reactions were negative, in 16.2 per cent there was a positive Dick and a negative Schick reaction and in 15.5 per cent a negative Dick and a positive Schick reaction. The table also shows the large number of pseudoreactions frequently seen in certain groups of individuals, especially in elder children and adults. Of the 589 children tested, 490 were found to be immune. Of these, 190, or 41.4 per cent, gave a pseudoreaction. The pseudoreactions due to the autolyzed bacterial substance of the streptococcus protein seem to be neutralized by convalescent serum, while those due to the other proteins are not neutralized by the serum.

Preventive Inoculations.—In the light of the newer work in scarlet fever preventive inoculations may be divided as in the case of diphtheria immunization into two forms: (a) passive; (b) active.

Passive Immunization with Scarlet Fever Toxins.—The antitoxic horse serum described recently by Dick and Dick has the power of neutralizing the streptococcus toxin in the proportion of 10 c.c. of serum to 50,000 skin test doses of toxin. Successful attempts have also been made to concentrate the antitoxin, as in the case of diphtheria antitoxin, by the addition of ammonium sulphate. The antitoxic serum should be injected in a dose of 10 c.c. into exposed children who show a positive Dick reaction. The dose of the concentrated serum would be proportionately less. The immunity is only temporary and thus corresponds to the diphtheria immunity following an injection of diphtheria antitoxin. The Dick test should be made first in exposed individuals as the results can be readily interpreted in twelve hours.

Attempts at passive immunization with convalescent scarlet fever serum have been recently reported by Smith and by Neff. The serum is injected subcutaneously or intramuscularly in doses of 15 to 30 c.c. and gives a temporary passive protection for several months. Such injections must be given as soon as possible after exposure. If injected two or three days after exposure, it may not be effective in preventing the development of scarlet fever. A quantity of pooled convalescent serum should be kept on hand so that it could be used in emergencies for prophylaxis and treatment.

Active Immunization with Scarlet Fever Toxins.—Where the exposure is not immediate and the danger not imminent, active immunity can be produced in susceptible children showing a positive Dick reaction. Such active immunity is conferred by injecting children under twelve years of age with 100, 250 and 250 skin test doses at intervals of from seven to ten days and individuals over twelve years with 100, 250 and 500 skin test doses. If the toxin for the skin test has to be diluted 1:1,000 and 0.1 c.c. used for the Dick test, then make a dilution of 1:20 for immunization and inject 0.2 c.c., 0.5 c.c. and 0.5 c.c. for children under twelve years, and 0.2 c.c., 0.5 c.c. and 1.0 c.c. for those over twelve years. Zingher recommended the use of the skin test dose as the best method for stating the amount of toxin injected for purposes of active immunization.

The injections are given intramuscularly into the triceps muscle. The local reactions vary in intensity, being, as with diphtheria toxin-antitoxin, more pronounced in older children and adults. The first dose is sometimes followed during the next day by a temporary slight indisposition, slight febrile reaction and even by a general scarlatiniform erythema. A slight sore-throat is also occasionally noted. These symptions disappear after from 24 to 48 hours. The second injection, even though increased two and a half times in amount, is followed by only slight local symptoms or by no symptoms. The Dick retest to determine active immunization is made at the end of two months.

TABLE 5

IMMUNITY RESULTS WITH SCARLET FEVER TOXIN (ZINGHER)

Under 12 years: 100, 250 and 250 skin test doses at weekly intervals.
DOSES GIVEN
Over 12 years: 100, 250 and 500 skin test doses at weekly intervals.
DICK RETEST AFTER 4 TO 5 WEEKS.

Institution	Per Cent Positive Dick at Original Test	Total Retested	Positive as in Original Test	Number Less Strongly Positive	Per Cent Less Strongly Positive	No.	Per Cent
Hebrew Orphan Asylum	29.2	143	19	20	14.0	104	72.7
New York Orphanage	44.4	91	10	36	39.5	45	49.4
Leake and Watts Home	22.0	40	12	10	25.0	18	45.0
Total		274	41	66	24.0	167	61.0

Table 5 shows the immunity results obtained by Zingher with scarlet fever toxin in 274 children injected in three institutions. Of the retested children 167 or 61 per cent showed that they had become immune. Most of the reactions noted were pseudoreactions. The large number of pseudoreactions indicates that a certain amount of protein hypersensitiveness developed after the toxin injections. Purification and concentration of toxin by the acetic acid method will eliminate most of the disturbing proteins. The table also shows that 66 of the injected children, or 24.0 per cent, gave positive reactions at the retest which were, however, much less pronounced than in the original Dick test.

Active immunization with the scarlet fever toxin will have to be carried out on an extensive scale similar to the work done in the immunization against diphtheria before definite conclusions could be reached as to its ultimate value. The results so far noted by Dick and Dick and by Zingher are very encouraging and indicate that an active immunity can be obtained in a large proportion of the injected individuals. The duration of this immunity remains to be determined. By analogy from the results noted in active diphtheria immunization with toxinantitoxin we may expect that the immunity will be more or less permanent. The initial active immunity probably lasts only one or two years. It is the subsequent exposure to repeated contact infection with the specific hemolytic streptococcus that will probably keep up the immunity. Similar exposure to repeated contact infection with the diphtheria bacillus is the important factor in the long duration of the active immunity to this disease, which now has been shown to continue for over 11 years.

Active Immunization with Blood from Scarlet Fever Case.—Recently Takahashi had the courage to immunize his five children with a minute amount of blood from an active case of scarlet fever. He injected 0.0001 c.c. of citrated blood subcutaneously into each child. No symptoms developed. Three of the children were tested for immunity fifty days later by the injection of a large amount (0.15 c.c.) of blood from an active case. The other two were tested one hundred and fifteen days later by smearing over the mucous membrane of the tonsils and throats a mixture of virus consisting of blood and throat secretions of a scarlet fever patient. He states that "for the next three weeks he carefully examined the temperatures, urine and throats of the children, but there was nothing to be noted at all. Thus the inoculation completely protected the children from the disease.

It is interesting to note in this connection that Dick and Dick have used whole blood and blood serum obtained from scarlet fever patients shortly after the onset of the disease and injected these substances in quantities varying from 0.5 c.c. to 5.0 c.c. into adult volunteers without producing any local or constitutional symptoms of scarlet fever. They also used filtered throat mucus with negative results.

Quarantine—Isolation.—In view of the fact that the transmissibility of the disease certainly begins early, a patient attacked by scarlet fever should be separated immediately from other members of the family. The question often arises in practice whether intercourse before or at the time the symptoms appeared has not been so intimate that such separation is useless, on the ground that the infection has already been acquired. The event shows that this is true in many instances, but not in many others; and, since no certain conclusion can be drawn in an individual case, and since the disease is a dangerous one, the benefit of the doubt must always be given to those who have been exposed, and further association with the patient should cease. On the other hand, those thus exposed must be viewed as suspects and kept apart from others.

The methods to be followed in the quarantining of the patient and the general safeguarding of others may well be given in fuller detail.

Requirements of the Sick Room.—Other things being equal, the room should be in the upper part of the house, in order to separate the patient as far as possible from other members of the household. This portion of the building is also farther from the noise of the street and of the house in general. Provision must be made for satisfactory heating and ventilation. This is usually, of necessity, such as the already existing construction of the building permits; but, when there is any choice in the matter, a room with a fireplace offers many advantages. Heating by oil stoves or gas stoves without direct conduction of the products of combustion to the outside air is a harmful method, while hot-water heating and steam heating make no provision for ventilation. Successful ventilation is well accomplished by the fireplace, if in use, as the draft produced by the heat draws air through the room from the windows. If no fire is kindled, inspection should be made to insure that the opening of the flue has not been closed by a slide or other cover, as is often the case. Ventilation may also be had through a window, care being taken to avoid direct drafts upon the patient, especially during convalescence. Window-board ventilation is very satisfactory. In other cases a frame covered with cheesecloth may be fitted in the window to allow free access of air while checking the rapidity of currents. Screens are of great value to protect the patient from direct drafts.

Nothing aids so greatly in the convenience of treating a case during isolation as the possibility of securing a sick room which communicates directly with another room, preferably a bathroom, this again opening into an entry. With this combination all doors into the sick room, except that from the anteroom, should be closed, and the cracks about them, as well as the keyholes, stuffed with raw cotton. The door from the anteroom into the entry should be kept closed except at the moments of the necessary gaining access to or leaving the sick room. At this door a sheet should be hung and kept moistened with a 5 per cent solution of carbolic acid or a 1:1,000 solution of corrosive sublimate. The likelihood of this procedure having any practical value is very questionable, in the light of what has been said earlier, since the disease is probably not spread by flying scales or by currents of air; but, in view of the uncertainty still prevailing, it is a wise precaution, as it can at least do no harm and is an additional reminder to the family and attendants that the disease is an infectious one. The windows in the anteroom should be kept open at all times, if possible, and the door from this room to the sick room generally closed. In this way the sick room is practically cut off from the rest of the house, except by what is in reality an out-of-door passage.

All pictures, carpets, curtains, and unnecessary articles of furniture, especially if upholstered, should be removed from the sick room, and all clothing not in actual use. Only such books or toys should remain to which no special value is attached, and which can be destroyed later. The nurse in attendance upon the patient should wear wash dresses and a rubber, oil silk, or washable covering for the hair. When it is necessary to leave the house, these garments, as well as the shoes, should be discarded in the anteroom, the clothing for out-of-doors put on, and the nurse pass directly out without intercourse with other members of the family. Before leaving the anteroom she should carefully disinfect her face, hands, and neck with a 2½ per cent solution of carbolic acid or with 50 per cent alcohol, and gargle her throat with an antiseptic solution, such as liquor antisepticus. It is better, as a rule, that she take her meals in the sick room or anteroom, rather than in the general dining room.

Others in necessary attendance should protect themselves and use disinfectants in a similar manner. The physician should remove his coat and don a washable gown which fastens closely about the neck and reaches to the floor. On his head he should wear a rubber or washable cap, and overshoes on the feet. When not in use these garments may with advantage be kept in a covered vessel, such as a metal bucket or porcelain jar with a lid, in which a small amount of formaldehyd solution has been placed. The disinfection of the thermometer, stethoscope, and other instruments should not be forgotten.

The food for the patient should be brought to the sheeted door of the anteroom by an attendant and left there for the nurse to take in. All dishes, spoons, and other eating utensils should be washed, and either allowed to soak for an hour in a 5 per cent solution of carbolic acid, or boiled. The bedclothing and that of the patient should in like manner be soaked in a 5 per cent carbolic acid, or a 1:1,000 sublimate solution, wrung out, and removed by an attendant from the door of the anteroom. In this condition they may be handled with impunity by any one and washed with the other household linen. As purchasing a large amount of 5 per cent carbolic acid solution is an expensive and inconvenient method, a strong stock solution should be prepared, such as the following: carbolic acid (Calvert's No. 4), 6 fluid ounces; glycerin, 4 fluid ounces. Adding 2½ fluid ounces of this to enough water to make a quart will give approximately a 5 per cent solution. It should be stirred thoroughly until the carbolic acid is entirely dissolved.

When the disease is over and the patient ready to be removed from quarantine, he should receive a thorough disinfecting sublimate bath of the strength of 1:10,000; and have his head washed well with another sublimate solution of the strength of 1:2,000. The throat is then to be gargled thoroughly with liquor antisepticus or other antiseptic fluid, the nose douched or sprayed with a saturated solution of boric acid, and the ears douched with the boric acid solution, or with one of 1:10,000 sublimate. He should then be removed to another room and dressed in fresh clothing. A final disinfection of the room follows; the floor and woodwork, and the walls, when unpapered, being scrubbed with soap and water and then with a 1:1,000 sublimate solution, and the room and its contents subjected to formaldehyd gas for at least twelve hours. The method of employment of this varies considerably. It is more efficacious if combined with steam if the contents of the room permit of this. The formalin candles or lamps are very satisfactory for family use where the local health boards do not attend to the matter. It is advisable, however, to use the tablets or the candles in at least double the number recommended by the makers. Papered walls had better be scraped and repapered. When it is possible to do so the mattresses and pillows should be removed and disinfected in a municipal steam sterilizing plant, and this applies also to the carpet, if of necessity it has remained on the floor. Fresh air and sunlight are great disinfectants. It is consequently advisable to allow the room after fumigation to be exposed to both these agencies for a week or more before it is reoccupied.

It is, in fact, questionable whether disinfection is of any greater value than thorough cleansing and exposure to the air. However, until the matter is settled, it is certainly advisable to follow every precaution possible.

In New York City the Department of Health has not only discontinued the terminal fumigation of the premises after scarlet fever, but also the fumigation of the rooms when a case is removed to the hospital during the infectious stage of the disease. It recommends, however, a thorough cleansing and, where necessary, renovation of the rooms.

Family.—As it is certain that the disease is spread especially through intercourse, all such must be forbidden as far as possible.

Other non-immune children of the family should at once be taken from the house, when this is feasible, and should be kept from school and from other children until such time as the outside limit of a possible incubative period is passed, lest they have the disease already developing in their systems. After this period there is no reason for treating them longer as suspects.

The father of a well-isolated patient, if not coming into contact in any way with the child, may continue to attend to his business—unless it is of a nature where he is thrown intimately with many young persons.

Even under this latter condition there is no special danger, but to avoid criticism it would be better that he change his residence temporarily.

Immune children who have already had the disease are in like manner not a source of danger if the patient is thoroughly separated from them; but for the same reason, if they continue to live in the house, they should avoid intercourse with other children until quarantine is removed.

Duration of Quarantine.—The necessary isolation is a matter much discussed. In the mild cases, without especial involvement of the throat and with no nasal or pharyngeal complications, it is probable that three weeks is sufficient.

In more severe cases six weeks is probably safer. When any nasal or oral discharge has continued, quarantine should be extended, and it is uncertain when safety can be assured.

In general in scarlet fever four to six weeks is probably a safe duration of quarantine, the former being, it would seem, just as safe as the latter period, which is the one most generally observed.

Prevention in Hospitals.—The method of checking the spread of the disease is a puzzling proposition which the hospital physician often encounters. When a case of scarlet fever develops in a general ward for children, the usual practice is to remove the patient at once to isolation. The other patients in the ward should be given the Dick test and, if positive, injected with antitoxic serum. The ward is quarantined for the maximum period of incubation, that is, seven days, and no new cases admitted. When, however, a number of cases break out in a ward, there would appear to be no question that the wisest course is to close it entirely for a time, and then disinfect it thoroughly. Sometimes, indeed, even after such disinfection, there appears to persist a remarkable tendency for fresh cases to develop from time to time.

Prevention in Schools.—The readiness with which scarlet fever is communicated before symptoms show themselves, to which reference has already been made in discussing the cause of the disease, renders the prevention of its spread in schools a matter of the greatest difficulty and uncertainty. To allow children to continue at a school where scarlet fever has appeared undoubtedly adds to the danger of their contracting it. On the other hand, to close a school on the development of a few cases interferes enormously with the education of the children in general without corresponding protection, as von Jürgensen has well pointed out, and is hardly a practicable procedure. He instances the closing of the schools in Tübingen for nearly a year and a half. The only method, both practicable and safe, seems to be at once to prohibit the attendance at school of all members of a class in which scarlet fever has made its appearance, thus keeping away those children who have been most closely associated with the patient, and who may be suspected of being in the incubative period. This applies equally well to day schools and to boarding schools. If the disease becomes at all epidemic, of course the closing of the whole school becomes an unfortunate necessity.

It is to be borne in mind that a general spread of the disease may be even fostered by the closing of a school, since the exposed and possibly already infected children are turned loose to mingle freely with their friends elsewhere.

Prevention in schools should follow along the lines so thoroughly laid out in diphtheria: the application of the Dick test for the selection of susceptible scholars, passive immunization for those intimately exposed, and active immunization with specific streptococcus toxin of susceptible individuals who are not in immediate danger. The test and active immunization should be preferably carried out as a routine measure in schools before there is any outbreak of scarlet fever.

During an epidemic of scarlet fever in a private school, in which 23 cases of the disease had developed among 125 pupils, the Dick test was applied by Zingher to 71 of the children, ranging in age between 12 and 18 years, and of these 51 or 71.8 per cent gave a positive reaction and 20 or 28.2 per cent gave a negative reaction. Of the 20 negative reactors 3 had had scarlet fever during the present outbreak and 3 gave a history of scarlet fever in childhood. These results indicate the high proportion of susceptible children among the more well-to-do classes in our population and correspond closely to similar observations made by Zingher with the Schick test for susceptibility to diphtheria.

Treatment of the Attack

Serum Treatment—1. *Antitoxin Horse Sera.*—Many attempts have been made to modify the course of scarlet fever by the use of specific sera. The results have been up to the present time far from uniformly satisfactory, and the opinions of those who have used them are greatly at variance. One of the earliest employed was Marmorek's antistreptococcic serum, applied by himself to the treatment of scarlet fever, on the ground that this disease was due to a streptococcus. Inasmuch, however, as the serum was one prepared from the streptococcus pyogenes derived from patients with other diseases than scarlet fever, theoretically the results could not be encouraging. Baginsky's experience with it was not satisfactory. Good results might with reason be hoped for in septic complications, and such, indeed, have repeatedly been reported. Later a serum was prepared by Aronson by the inoculation of horses with streptococci derived from various sources from patients with scarlet fever. Various other sera have been employed, as for instance the one prepared by Moser, by a method somewhat similar to that used by Aronson, except that cultures were made from the blood of scarlet fever patients, and horses inoculated with these. The serum was thus of a polyvalent nature. The value of the treatment has been maintained by many, among them Escherich and others. Heubner and Ganghofner contend that no good results follow. The antistreptococcic serum prepared by Menzer was tried in scarlet fever by Heubner, but without encouraging results.

Recently Dick and Dick have described an antitoxic serum obtained by injecting horses with the toxic filtrate from a scarlatinal hemolytic streptococcus culture. According to their statement 10 c.c. will neutralize 50,000 times the amount of toxin used for the skin test. Clinical results are not reported. Dochez has also described a special method for obtaining an antitoxic horse serum. He injects liquefied agar into the cellular tissue of the animal's neck. After the agar solidifies, the sedimented bacterial mass of a scarlatinal streptococcus culture is injected into the center of the agar. The toxins produced by the organism pass into the circulation and stimulate the production of antitoxic antibodies. One of the objectionable features to this method of animal inoculation is that a large sloughing ulcer is produced at the site of the injected mass which is discharged as a foreign body. Blake and his associates describe good clinical results obtained with this serum. The dose recommended is 50 c.c. injected intramuscularly. Observations made at the Willard Parker Hospital with Dochez serum indicate that the serum has antitoxic value, but does not protect against the secondary septic complications, such as glands, ears, etc.

Injections of antitoxic sera obtained from horses will no doubt sooner or later become a routine measure in the treatment of scarlet fever. It is not only the severe toxic cases that should be treated with antitoxic serum, but also the milder cases that apparently recover so promptly. Many of these cases are known to be followed by late complications and sequelæ of scarlet fever. Among these complications nephritis should be especially mentioned. It is possible that by the injection of antitoxic serum in the early stages of the disease many of these late complications will be avoided.

2. *Convalescent Human Serum.*—The injection of blood serum derived directly from patients convalescing from scarlet fever has been recommended by Roger, Weissbecker, Huber and Blumenthal and Leyden. This method of treatment was not seriously taken up, however, until 1912, when Reiss and Jungman recommended the intravenous injection of large amounts (50 to 100 c.c.) of pooled convalescent serum. Koch treated a series of cases by the same method and obtained similar good results. In the United States, Zingher was the first who reported a series of cases treated with convalescent blood. He recommends the intramuscular injection of freshly drawn whole blood obtained from donors from the second to fourth week of convalescence.

The method of obtaining the blood and its injection is very simple. From 120 to 300 c.c. of blood is drawn by means of a 30 c.c. Record syringe and a No. 17 gage needle from the median cephalic vein of the donor at the bend of the elbow and immediately citrated by adding the blood to a 10 per cent solution of sodium citrate in the proportion of 30 c.c. of blood to each cubic centimeter of the citrate solution. This makes the final dilution of the citrate 0.33 per cent. The blood is collected in 100 c.c. bottles, each of which contains 2 c.c. of the 10 per cent citrate solution. To each bottle 60 c.c. of blood is added, the blood being shaken after each addition to distribute the sodium citrate solution.

The blood is injected into the following regions: triceps, outer regions of both thighs (vastus externus), the calves (soleus) and both gluteal regions. In young children 15 c.c., and in older children and adults 30 c.c., is injected into each of these muscles. The total amount depends on the age of the individual, varying from 120 to 240 c.c. The blood serum is rapidly absorbed as shown by the soft and supple condition of the muscles on the following day, when they will be found to have regained their former size and consistence.

The scarcity of the supply of convalescent serum or whole blood indicates that this method of treatment should be reserved for the early toxic and malignant cases of scarlet fever, which are seen between the third and fourth day of the disease. Such patients show the clinical picture of restlessness and delirium, an intense purple or petechial rash, moderate glandular enlargement and severe angina with a slight exudate over the tonsils, uvula and pillars of the fauces. The effect of convalescent blood in these early toxic and malignant cases of scarlet fever is seen in a critical drop in temperature beginning about six hours after injection and ending in from twenty-four to thirty hours. The temperature often reaches normal and will remain nearly normal in the majority of the cases; in others, especially where complicated with severe tonsillar and faucial exudate associated with inflamed cervical glands, the temperature may rise again in a few days, but rarely to the same height as at the time of injection. Other results which are quite as striking can be seen in the early fading of the rash, the improvement in the circulation and the

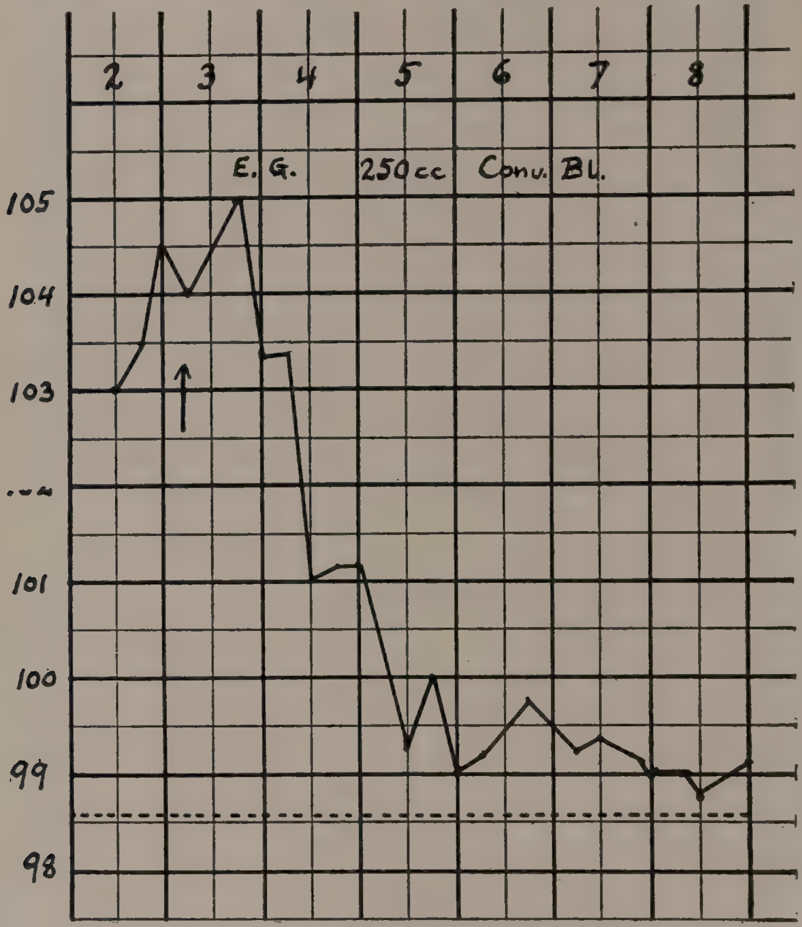

FIG. 1.—CASE OF E. G., YOUNG MAN NINETEEN YEARS OF AGE.

character of the pulse, the general condition and mental symptoms. The delirium will frequently disappear and the clinical eye detect that general improvement, which is so difficult to interpret by a mere temperature, pulse and respiration record.

The following 3 cases treated at the Willard Parker Hospital will

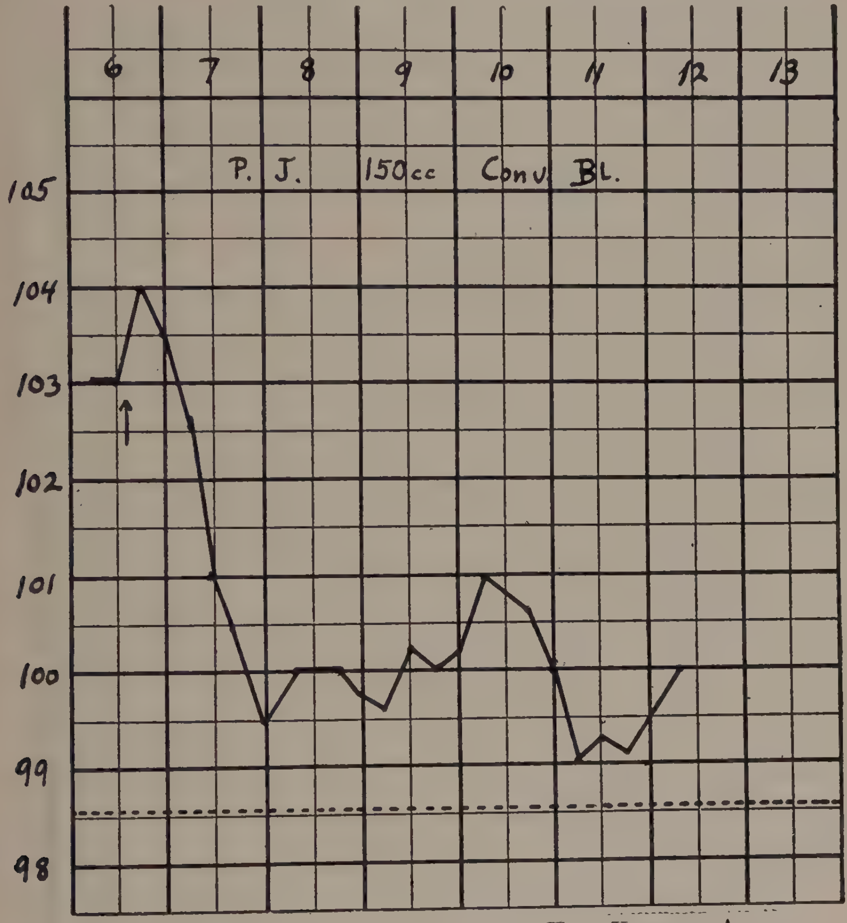

Fig. 2.—Case of P. J., Boy Six and One-Half Years of Age.

illustrate the effect of the intramuscular injections of whole convalescent blood:

Case 1.—E. G. (Chart 1), a young man, 19 years of age, admitted on the second and injected on the third day of the disease. Very toxic and delirious. Two hundred and fifty c.c. of blood caused a critical drop in temperature from 105° F. to 99° F. associated with a clearing up of the delirium and a distinct improvement in the character of the pulse.

Case 2.—P. J. (Chart 2), a boy 6½ years of age, admitted on the sixth day of illness. Intense rash, very restless, toxic and delirious. The injection of 150 c.c. of convalescent blood caused a critical fall in temperature from 104° F. to 99° F. during the next twenty-four hours. The mental symptoms cleared up rapidly and the rash faded in a short time.

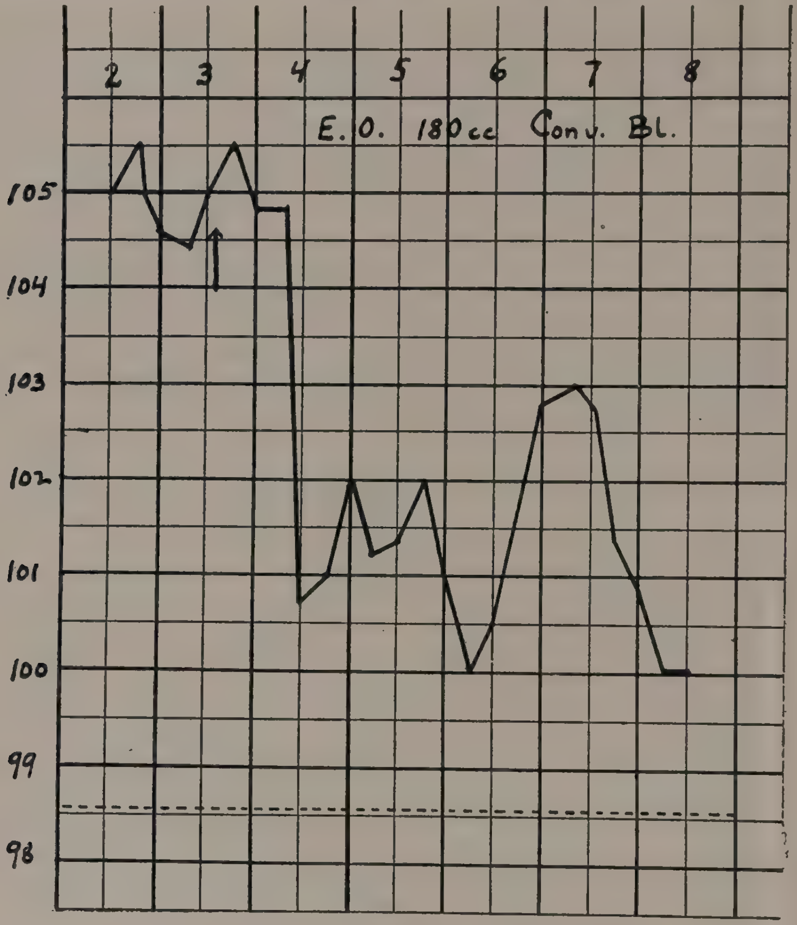

FIG. 3.—CASE OF E. O., GIRL TEN YEARS OF AGE.

Case 3.—E. O. (Chart 3), a girl 10 years of age, admitted on the second day of the disease and injected on the third day with 180 c.c. convalescent blood. Here also was noted a critical drop in temperature from 105° F. to 100.5° F. in less than eighteen hours, associated with a marked improvement in the general condition and especially the delirium. A streptococcus exudate, present on admission, continued for a few days and gave rise to subsequent temperature excursions. The patient made an uneventful recovery.

The donors should be free from syphilis and tuberculosis. A record of individuals who are willing to act as donors should be kept by the authorities in charge of contagious disease hospitals. Convalescent blood or serum will deteriorate after a month when kept in the ice-box and it is, therefore, preferable, to use only fresh blood. The question of using donors who are several months or even several years convalescent should be considered and tried on a large scale. If such blood is as effective as that of more recent convalescents, it would help considerably in increasing the supply of available donors.

Weaver reported excellent results in two series of cases treated by the intramuscular injection of pooled convalescent serum. Similar favorable results have been reported by Smith, Bernbaum, Kling and Widfelt, Bode and Griesbach.

In the later septic cases of scarlet fever seen after the fifth or sixth day of the disease, Zingher recommends that, where no convalescent blood or antitoxic blood from horses is obtainable, the sick children be injected with fresh normal blood obtained from one or both of the parents if they give a negative Dick reaction. The cases included in this group are those in which the rash may have faded entirely, but the membranous exudate over the fauces and tonsils is severe and extensive and often appears necrotic. The cervical glands are enlarged and tender. The temperature is high and septic in character, the pulse proportionately small and rapid. Such injections may have to be repeated once or twice at intervals of from four to five days. These injections of normal citrated blood may not have much specific action; but the nutritive and stimulating properties and normal antibody content of relatively large amounts of normal blood have shown definite beneficial results in some desperately ill cases of septic scarlet fever.

General Hygienic Measures.—Hygienic measures are first to be considered. The selection of the room has already been discussed to a certain extent. The temperature should be not over 60° to 65° F. during the febrile stage, and even after this it is better to keep the room reasonably cool and the patient warm in other ways. Fresh air is essential, but it is important to avoid direct drafts upon the patient, since various complications may follow. This applies, however, chiefly to convalescence, as during the existence of fever it is difficult to effect any dangerous chilling of the patient. The obtaining of fresh air without drafts is, however, a matter easily managed. Reference has already been made to this (page 254). The coverings on the bed should be light during the febrile stage. Later they may be those most comfortable to the patient. Ablution should be given at least once every day. There was never good reason for the once common practice of allowing a scarlet fever patient to pass days or weeks without bathing. Even when fever has ceased there is no possible danger of chilling if the ablution is performed carefully under the bedclothes, or with the uncovering of but one part at a time. The diet should be light, milk constituting the major portion of it. The diuretic effect of milk is excellent, and relieves greatly the strain thrown on the kidneys in this disease. Where milk is refused or is taken in insufficient quantities, cereal porridges may be employed. Digestible fruits are at all times permissible. In fact, throughout the attack it is important that the patient be not underfed. The giving of meat and eggs, however, is, in my opinion, better delayed until at least after two weeks of the illness have passed. It is important also to ensure that water be taken very freely. This may be either plain or carbonated, or one of the alkaline mineral waters, such as Vichy. In severe cases, where food is refused on account of difficulty in swallowing, or as a result of the unconscious or delirious state, feeding by rectal injection or gavage may be necessary. Under these circumstances the diet ordinarily to be preferred may have to be abandoned and the food administered in concentrated form. Some investigators, among them Gerstley, believe that the administration of a diet containing the ordinary amount of meat has no influence in increasing the number of cases of nephritis.

At the Willard Parker Hospital the diet consists of milk alone during the first week of the disease, of milk, broth and cereals during the second week, and of milk, thickened soups, cereals, toast or bread and butter and stewed fruit during the third week. During the fourth week this diet is continued with the addition of one or two eggs a day.

It has long been a common practice to order a daily inunction with carbolized oil (10 or 20 gr. to 1 oz.), with the idea of disinfecting the skin and thus checking the spread of the disease to others. If the scales are as little harmful as is now maintained, this is not necessary. It may, however, be of service in allaying the itching, which is often troublesome. In the case of little children the susceptibility to carbolic acid and the danger of poisonous absorption must be borne in mind. In such cases a weak thymol ointment (1 per cent) may be substituted if inunction is desired. A daily inspection of the mouth, throat, and nose should be made, in order to prescribe appropriate treatment at once if indicated. The urine should be examined every one or two days for at least three weeks. Rest in bed must be insisted upon even in the mildest cases for ten days to two weeks, and in average ones certainly for three weeks in order to avert as far as possible irritation of the kidneys by bodily exercise, and to lessen the danger of a postscarlatinal nephritis.

Inasmuch as there is reason to believe that cases of scarlet fever with septic manifestations are capable of transmitting this secondary infection to others with the primary disease, the separating of these cases from others is desirable. It would appear, in fact, as though we were dealing with two disorders—that due to the primary scarlatinal toxin, and that depending upon streptococcic involvement productive of complications.

General Medical Treatment in Average Cases.—Little internal medication is required in ordinary cases. Many drugs have been recommended as more or less specific. Illingworth believed that the biniodid of mercury would cut short the attack and cause the rash to disappear rapidly, and this opinion was supported by Dukes. Mehary upheld the abortive power of salicin. Curgenven supported others who believed in the mitigating influence of inunctions of oil of eucalyptus, and Ross thought that decoction of cinnamon could abort an attack. Other drugs have been recommended from time to time, but there is no positive evidence that any of them possess real value.

The dietetic regimen prescribed and the ingestion of plenty of water may be sufficient to maintain diuresis. In addition a febrifuge and diuretic may be ordered containing, for instance, spirits of nitrous ether, potassium citrate, ammonium acetate, or potassium bitartrate, but no drug which can be irritating to the kidneys. There is no particular value in chlorate of potash in this disease, and it is a remedy capable of doing harm. Warm tub baths are useful to relieve nervousness or restlessness, or to reduce temperature. Stimulants are not required. If the patient is old enough he should employ an antiseptic gargle frequently, such as liquor antisepticus, or permanganate of potash (1: 8,000). In the efforts to medicate the throat as well as to promote diuresis, the older, well-established custom may well be followed of administering every one or two hours small doses of the tincture of the chlorid of iron, directing that, although the mouth may be washed afterward, no water may be swallowed immediately. This allows the astringent and distinctly antiseptic chlorid of iron to remain in contact with the throat much of the time.

Nothing is to be gained and much discomfort is caused by overdosing in this disease. The treatment must be purely symptomatic. This brings us naturally to the consideration of the therapeutics of special symptoms, one or more of which may be much intensified in the severer cases. Some of the conditions to be described under complications might readily be spoken of here. In fact the demarcation between complications and symptoms cannot be very closely drawn.

Fever.—Moderate elevation of temperature reaching 103° or 104° F. and lasting but a few days is never of itself a sufficient cause for alarm. It is not so much the height of the temperature as the effect upon the system which demands attention. The employment of hydrotherapeutic measures is generally to be preferred to the administration of drugs if the element of temperature requires active treatment. Sponging with warm water of 90° to 100° F., with or without the addition of alcohol, is often effective, and certainly adds greatly to the comfort of the patient. It must be done thoroughly in order to make it successful in reducing temperature. The bed covers and the greater part of the body clothing should be removed and the patient placed upon a blanket, under which is a rubber protection for the bed. The water should be applied freely, beginning with the head, and the process continued for ten or fifteen minutes, and repeated every three hours or oftener. When water of this temperature is not efficacious, cooler water may be used of a temperature of 65° to 80° F., depending upon the case. It is always essential that a good reaction be obtained. If the patient remain cold for any length of time, with blueness of the hands and lips and feebleness of the pulse, the procedure does more harm than good.

Then, too, in the case of children of an age where the application of sponging, even when warm, is often unpleasant and occasions crying throughout the process, the length of time required is a distinct disadvantage. The administration of a warm tub bath is then often not only more grateful, but more efficacious as well, and requires a shorter time. The child is undressed and placed in a bath of 90° to 100° F., where he stays a varying time, averaging five minutes, according to the effect produced. He is then removed from the bath, given a very hasty and imperfect drying, enveloped loosely, including the arms, in a blanket pinned under the chin, and put in bed. Here he may be allowed to sleep if he will, while meantime the antipyretic effect continues in favorable cases. Later, in an hour or so, the blanket is removed and the child dried and put into his night clothes. Where there is decided hyperpyrexia with threatening nervous symptoms, more vigorous procedures may be needed. Here a cool bath of 70° F. may be indicated, or in older, more vigorous subjects, very exceptionally one colder than this.

The warm or cold pack is in many instances more efficacious than the tub bath and better tolerated. It needs to be frequently repeated. Generally it is given in the usual way, namely, wrapping the patient in a sheet wrung out in water, and then, with this in position, wrapping him in a blanket. Should the temperature be alarmingly high, the blanket is not used, but folded towels are dipped in very cold water, pressed out, applied over the patient's body, and redipped and reapplied at short intervals. The cold pack used in this manner is a powerful antipyretic measure and should be used with care. In fact, a caution must be given with regard to all antipyretic procedures. They must never be used as routine measures, simply because a temperature is high, and they must be carefully adapted to each case, which should be in the meantime carefully watched. The existence of decided cardiac weakness is a contra-indication to cool baths, and often to baths of a higher temperature.

It must be remembered that patients in early childhood and especially in infancy usually tolerate cool water badly in any febrile disorder, and warm water is equally serviceable and less dangerous.

Occasionally the need arises for the reduction of temperature in cases where hydrotherapy cannot be employed. Under such circumstances antipyrin or phenacetin may be given, but the effect must be carefully watched. These drugs are usually not depressing in afebrile states, but frequently do cause unfavorable results if febrile temperature be lowered by them too rapidly or too greatly. They should be given in small doses frequently repeated until the desired result is obtained. There are times when they are very serviceable, but these are the exceptions. The inunction of guaiacol carbonate upon the abdomen is also capable of producing reduction of temperature, but often too energetically and unsafely.

Cerebral and Other Nervous Symptoms.—What has just been said regarding the treatment of high temperatures applies here as well, since it is generally in the relief of nervous symptoms accompanying fever that hydrotherapy finds its greatest value. In addition, an ice-cap may be applied to the head in the effort to allay nervous excitement, but the effect seems very uncertain, except in infancy, where the depression produced by it is sometimes too great. For restlessness, jactitation, and symptoms of impending convulsions the warm bath of 100° F. is often extremely useful, even when decided fever is present. The bromids, veronal, and sometimes opium are of benefit if restlessness and sleeplessness are great. It is only when decided hyperpyrexia is attended by dangerous cerebral symptoms that the cool bath is to be employed in early life. The coal-tar preparations often fill a useful place in the relief of nervous manifestations, even when no special elevation of temperature is present. Delirium, stupor, jactitation, grinding of the teeth, and similar symptoms are often relieved by them in a manner which cannot be satisfactorily explained by the mere reduction of temperature. Nevertheless, the need for this treatment is not frequent, and the danger of too decided a fall of temperature and consequent prostration must never be forgotten.

Cardiac Weakness.—A condition characterized by rapid, feeble heart-sounds and pulse, and by coldness and cyanosis of the extremities, demands stimulation. How energetic this shall be depends always on the needs of the case, and these must be carefully considered, as both understimulation and overstimulation are to be deprecated. Alcohol in some form is one of the most rapid and satisfactory stimulants. Camphor dissolved in almond oil (1:10) and given hypodermically is a powerful and quickly acting remedy in urgent cases.[1] Digitalis is invaluable, but takes a day or more before much good can be expected from it, as shown by the experiments of Hale, and earlier by many others. The tincture is probably the best preparation, but the strength of this varies greatly. Strychnin is a useful tonic and stimulant, but must not be pushed to the extent of increasing restlessness and sleeplessness, and is always to be avoided when there are symptoms present pointing toward convulsions. Nitroglycerin is an excellent and prompt remedy in urgent indications of cardiac failure. The effect is, however, transitory, and the dose must be frequently repeated while the need for it lasts.

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[1] In a large experience in scarlet fever, I have found the double salts of caffein or adrenalin very efficacious in acute myocardial insufficiency in the acute infectious diseases. They should be given hypodermically, first the adrenalin and then, because its effects are more lasting, the caffein. When necessary, venous infusion of a normal salt solution containing the requisite dose should be done. This is reserved for the most urgent cases.—Editor.

A poorly developed eruption is a common attendant of debility depending upon cardiac weakness. The old practice of giving a hot bath to bring out the rash was often a good one; not that the recession of the rash in itself was a matter of any moment, but that it was an index of imperfect peripheral circulation which the hot bath tended to relieve.

Sepsis.—Sepsis develops generally from a local lesion of the throat, as seen in anginose scarlet fever, and the constitutional involvement may be at first, or remain, not great. In other cases there is early evidence of widespread septic poisoning. The treatment must be supporting and stimulating. As forms of streptococci are the cause of the condition, it is here particularly that the antistreptococcic serum should offer the greatest hope of benefit. The results so far, however, have not been very encouraging in these secondary septic complications of scarlet fever. This holds true for the newer antitoxic sera as well as for the older antibacterial sera, such as Moser's. Hypodermoclysis, enteroclysis, and even intravenous injection of a physiological salt solution are indicated in the effort to eliminate the toxins from the system.

Treatment of Convalescence.—Apart from the care in the matter of exercise, diet, and exposure already referred to, patients during convalescence frequently require tonic treatment for a degree of debility which often continues, and which is quite decided after severe cases. Change of air is now one of the best remedies, selecting by preference localities where the patient can be in the open air the greater portion of the day. The anemia which often remains demands iron in some form for a considerable time. Strychnin, too, is a serviceable general tonic.

Arsphenamine Treatment.—It would seem but natural that the treatment by arsenical preparations, such as Arsphenamin, should be attempted in scarlet fever. The Wassermann reaction is occasionally positive in this disease. Arsphenamin has also been used with some success in severe necrotic inflammations of the throat, such as Vincent's angina, and in some of the protozoön diseases. Several investigators have tried this treatment, which seems to have favorable influence in severe throat conditions, probably because they are contributed to by the spirochetes found in the mouth. Otherwise the medication has doubtful value.

Tonsillectomy.—The removal of the tonsils during the acute stage of scarlet fever when the tissues are infiltrated and rigid would seem to be fraught with danger and would not as a rule appeal as a justifiable procedure to the surgical instinct of the practitioner of medicine. Yet Place has obtained favorable results and recommends the removal of the tonsils, not only during convalescence from scarlet fever, but also during the early acute stage of the disease. He states that there is reason to believe that early operation in scarlet fever tends to reduce the danger of complications. Bullowa also thinks that the patients seem to have a better chance if the pressure on the tonsils is relieved by incision of the plica or the focus of infection in the throat is removed by tonsillectomy.

TREATMENT OF COMPLICATIONS AND SEQUELÆ

Affections of the Throat and Nose.—Involvement of the throat in moderate or slight severity so consistently constitutes a manifestation of the disease that it might well be considered under symptomatology. When severe enough to demand special treatment, the nasal and pharyngeal conditions are rather to be regarded as complications. As in the case of all complications of scarlet fever, prevention is to be attempted in every way possible. The systematic spraying of the throat with antiseptic solutions and the use of antiseptic gargles aid greatly in hindering the development of streptococcic invasion of these mucous membranes. When evidences of rhinitis are already present, the nose should be sprayed or syringed several times a day with a mild, warm solution of boric acid, a very weak solution of salicylic acid or thymol, or even with a warm normal saline solution. The syringing must be done with gentleness, avoiding the forcing of septic material into the eustachian tube, with consequent infection of the ears. Pseudodiphtheritic (streptococcic) involvement of the fauces often requires more energetic local treatment. Gargling is now inefficacious, even if the patient were well enough to perform it thoroughly. Remedies are best applied directly, every two to three hours, with a spray or on a swab of cotton wrapped firmly on an applicator, which is more satisfactory than the ordinary camel's hair brush. Diluted peroxid of hydrogen (1:2) is an excellent cleansing, antiseptic substance, care being taken that a preparation is chosen free from decided acidity. In many cases, where no large amount of membrane has formed, this alone is sufficient, the treatment being repeated every three to six hours. Other suitable applications for swabbing are permanganate of potash (1:40) and corrosive sublimate (1:5,000); and one of the best is diluted tincture of the chlorid of iron (Tr. ferri chloridi, 1; glycerinum, 1; aqua, 2).

Nitrate of silver in solution (5 or 10 gr. to 1 oz.) is employed by many, and some of the newer preparations of silver are also useful.

In addition to the means described, the use of ice-bags over the region of the tonsils and the frequent sucking of ice aid decidedly in limiting the degree of inflammation and relieving pain.

Always in making applications to the throat the exhaustion which follows the struggle of a rebellious patient must be balanced against the good which the treatment may produce, and this is a matter which requires careful consideration and sound judgment. When inadvisable to paint the throat, reliance must be placed upon atomization, employing peroxid of hydrogen or such solutions as those recommended for the nose.

Sloughing of the tonsils requires the repeated application of powerful disinfectant solutions, such as the tincture of the chlorid of iron, best in the form of Loeffler's solution with toluol, or the employment of cauterization. True diphtheritic involvement of the fauces and nose is a complication of sufficient frequency to influence many fever hospitals to give routinely diphtheria antitoxin to all scarlet fever patients. Should any pseudomembrane develop in a case of scarlet fever, the case should be treated as an ordinary one of diphtheria, even without waiting for the result of the culture, which should be taken promptly.

As previously mentioned, salvarsan and neosalvarsan exercise favorable influence in some of these cases. The dosage varies from 0.15 to 0.45 gm. of neosalvarsan. Three or four doses may be given on successive days. More than 0.8 gm. should seldom be given in three days.

Severe anginose symptoms in scarlet fever always constitute a serious complication of the disease, and demand, besides the local measures described, vigorous supporting treatment. They are, in fact, a local septic manifestation with more or less general septic involvement. Swallowing is frequently difficult and always painful, and much persuasion may be required to make the patient take sufficient nourishment. It may consequently become necessary to give all food in a concentrated form, or even to employ rectal feeding or to use gavage.

Otitis.—This is a frequent complication and sequel of scarlet fever found by Pugh in 15 per cent of 11,000 cases, and by Gordon in 19.5 per cent of 8,695 cases. These figures are exclusive of the cases in which there is merely slight pain in the ears. Avoidance of the disorder is, therefore, to be sought from the outset of the attack of scarlet fever. Faithful disinfection of the throat and nose in the manner already described doubtless will prevent the disease in many instances. The wearing of a flannel cap covering the ears is also advised, with the intent of equalizing the circulation through this region. Should otitis develop, as shown by the increase of temperature and by severe pain and tenderness, the cap should certainly be applied and a hot-water bag kept in apposition to the ear. Douching the canal with water as hot as can be borne with comfort aids in relieving the congestion. The instillation of a few drops of a solution of adrenalin chlorid or of a 4 per cent cocain solution is also often successful in relieving pain. The process is, however, very liable to advance to suppuration, and perforation occurs if paracentesis has not been required for the relief of pain before the discharge takes place of itself. In quite young patients it not infrequently happens that the diagnosis of otitis is not made, owing to the absence of definite complaint, and treatment cannot be employed until perforation and discharge of pus occur. After perforation the treatment is that for suppurative otitis in general, the chief object being to maintain the canal in an aseptic state. The possibility of the development of mastoid abscess is always to be borne in mind, since prompt surgical interference may be required in this event.

Cervical Adenitis.—A moderate enlargement of the glands is nearly always present when inflammation of the throat is a decided symptom. This occurs early, and not infrequently becomes later a condition demanding treatment. In the severe anginose cases an extensive inflammation of the glands and surrounding cellular tissue may take place early, producing, it may be, great swelling of the neck. The condition may become a gravely septic one. Ordinarily adenitis sufficient to constitute a complication or sequel occurs later in the disease. Schick reports it a sequel in 7.2 per cent of 900 cases, and Caiger and Dudgeon in 11.4 per cent of 10,983 cases. In the milder cases resolution takes place of itself, or may be favored by the continued application of an ice-bag, with, however, a layer of cloth between the bag and the skin. In other cases iodin or ichthyol is successful in checking the process. Painting the glandular region with a thin layer of flexible collodion has also been found useful through the pressure which it exerts. Tonic treatment, especially with iron and strychnin, is indicated also in these cases. Where pus is evidently forming, the pain is best relieved by hot applications, which hasten the process and thus curtail the duration of suffering. The pus should be evacuated as soon as it approaches the surface. Nothing much is gained in these cases by an early, deep incision, since, if destruction of the gland has already begun, it will continue until it is entirely broken down and discharged. By this is not meant that a large amount of pus should be allowed to accumulate before being evacuated. In the gravest cases, where early extensive inflammation of the glands with cellulitis attends severe anginose scarlet fever, prompt and free incision is indicated if pus is being formed, or even without waiting for certain indications of this (Angina Ludovici).

Gastro-intestinal Complications.—Digestive disturbances are not, as a rule, troublesome. Diarrhea is a frequent complication, but seldom of an inflammatory nature, and treatment is usually not required, and in any case is that for mild diarrhea of catarrhal origin, such as the administration of bismuth, or perhaps opium. The tendency to diarrhea in this disease is, however, a warning not to use purgatives too freely early in the case. Constipation sometimes requires treatment, but is best relieved by suppositories or injections. The initial vomiting which ushers in the disease usually disappears promptly. In some cases, however, it may persist very obstinately. In this event carbonated water, cracked ice

—which should be swallowed, not sucked—equal parts of limewater and cinnamon water, or similar preparations may be employed. Occurring later, vomiting is oftenest a symptom of uremia, and will be referred to in considering nephritis.

Arthritis.—This is seen as a complication or sequel in very varying frequency: 2.4 per cent in 500 cases reported by Ashby; 19.1 per cent of 1,000 cases recorded by Herberg. Whether or not it is at all rheumatic in nature is disputed, and this renders the treatment very uncertain. Nevertheless, the administration of salicylates may well be tried, together with the application of protective dressings to the affected joints. In the more unusual septic cases, where suppuration follows, surgical measures are often called for.

Some cases of arthritis, complicating scarlet fever, are due to the gonococcus. These joints are especially apt to show a more marked periarticular swelling. Bullowa observed 14 cases of joint involvement in children at the Willard Parker Hospital in which the complement-fixation test for gonorrhea was strongly positive. In some of these children the blood culture was also positive (Zingher). The gonococcus may be found in the blood without any mucous membrane discharge. Gonococcus joints are frequently persistent and should be treated with large doses of vaccine and immobilization by splints.

In a number of cases of acute arthritis in scarlet fever, a curious septic rash precedes the appearance of the joint symptoms by from twenty-four to thirty-six hours. This rash is found scattered over the trunk and limbs, is not very profuse and is not especially seen near the involved joints. It consists of small macules, about 0.25 to 0.5 cm. in diameter, with a tiny central vesicle that might be mistaken for chicken-pox. The rash is found more frequently in children with gonococcus arthritis than in those with the ordinary form of arthritis.

Nephritis.—Involvement of the kidneys is one of the most dangerous complications and sequels of scarlet fever, and a frequent one. Omitting from consideration the slight albuminuria with cylindroids and hyalin casts, which is liable to occur in any febrile infective disorder, the frequency of nephritis seems to vary with the epidemic. Ashby found it in 6 per cent of the cases; Caiger and Dudgeon in 4 per cent of 10,983 cases; Royer in 7.76 per cent of 756 cases. The renal complication is most probably caused by the action of the toxin upon the kidneys during the early stages of the disease. It occurs certainly often enough to make it a serious consideration whether the antitoxic serum obtained by injecting horses with the toxin of the scarlatinal hemolytic streptococcus should not be used as a routine in the early stages of every case of scarlet fever, even in the very mild forms of the disease. The etiological influence of exposure to cold is questioned by many authorities and has certainly been overrated. As, however, local surface chilling undoubtedly increases the hyperemia of the kidneys, there seems no reason why this should not favor the action of any germs or toxins upon these organs. All such exposure is, therefore, certainly to be avoided as long as any doubt continues regarding the etiology. These remarks apply principally to surface chilling after fever has disappeared. During pyrexia it is, as previously stated, doubtful whether patients can be given "cold" in this way. In the same way, rest in bed and the consumption of an unirritating diet lessen the work which the kidneys are called upon to perform, through the action of these procedures in diminishing the energy of the metabolic processes of the body. The employment of diuretic remedies as preventive measures has already been referred to. Royer found that the administration of chloral, previously recommended by others, lessened the incidence of nephritis. Urotropin, first advocated by Widowitz for the same purpose, has been highly praised by Buttersack, Patschkowski, and H. P. Thompson. Garlipp has not found it serviceable. Further studies are needed. On theoretical grounds the drug should prove of value. The employment of turpentine for the same purpose was urged by Tobietz. A salt-free diet was advocated as a preventive of nephritis by Deléarde, confirming the earlier report upon it by Guinon and Pater, but the experience of Nobecourt and Merklen found it not equal to a milk diet for this purpose.

Nephritis actually developed may show itself in several ways and demands corresponding variations in the method of treatment to be employed. There may be a sudden onset of moderate edema of the eyelids, hands, and feet; fever; and scanty, high-colored urine, but no nervous symptoms of note. In such cases the use of mild diuretics, such as acetate of potash or citrate of potash, the administration of saline purgatives in moderate doses, and the employment of warm baths and of large, warm, saline enemata, is of service in maintaining the action of the kidneys and in supplementing this by favoring excretion through the bowels and the skin. The diet should consist solely of milk. Large amounts of water should be taken. A useful drink to give is the so-called "imperial drink," which is made by dissolving a dram of cream of tartar in a pint of boiling water, and flavoring with lemon juice and sugar. The mixture is allowed to cool before use. Barley water may also be used. Rest in bed must be absolute. It is important that the bed be well warmed before the patient is returned to it after the warm bath, and that he be well covered while in bed. The baths may be given once or twice daily and last fifteen minutes or longer.

In severer cases symptoms similar to those described occur, to which are added those of decided uremia; or the urine may exhibit the gross appearance of a true hematuria. Vomiting, convulsions, and similar symptoms develop. Dry cups over the kidneys are of service, or even wet cups, if the suppression of urine is nearly complete. The hot-air bath or vapor bath now fills a very useful purpose; or the patient is put into a hot bath of 100° to 105°, left there a few minutes, and then removed and enveloped in hot blankets without drying. This tends to produce profuse perspiration. Pilocarpin is a useful remedy for adults, but is dangerously depressant for children. Both Allaria and Sheffield have seen the convulsions of scarlatinal uremia relieved by lumbar puncture. The latter writer employs also hypodermic injections of morphin and atropin. Vomiting is relieved principally by reëstablishing the action of the kidneys. Von Jürgensen recommends for it minute doses of tincture of iodin. In cases of hematuria, in which sufficient blood is lost to demand treatment, ergot or calcium chlorid may be tried, and later the continued administration of iron, as in Basham's mixture.

The most common complex of symptoms in scarlatinal nephritis, however, is that appearing in the third or fourth week of the disease. Although evidences of uremia may appear here also, the most prominent manifestations are usually those of dropsy. There develops a widespread dropsy, perhaps involving the serous cavities as well. Generally the onset is insidious and the development of symptoms gradual. In the acute stage of this "postscarlatinal nephritis" the treatment is very similar to that spoken of for the nephritis occurring earlier in the disease, except that special attention must be given to the removal of dropsy by purgation and sweating. Relief of the serous cavities by tapping may be required.

When in any case of nephritis well-marked symptoms of uremia develop, very energetic treatment is needed, including free sweating with hot packs and vapor baths or hot-air baths and free purgation. To effect the latter, powerful drugs are sometimes needed, such as croton oil or elaterium. Neither of these is suitable in childhood.

In most cases where the nephritis is becoming subacute or chronic, there is a tendency for anemia to develop and for more or less dropsy to continue. Here a combination of iron with a diuretic is useful, and Basham's mixture answers satisfactorily. Digitalis is often required to aid an overtaxed heart, and nitroglycerin may lessen the high arterial tension. Hot baths or packs or the vapor bath or hot-air bath are serviceable in proportion to the degree of dropsy. Such drugs as spartein, diuretin, and theocin are often of great value in this stage. The diet in the chronic form of nephritis should be solely or chiefly of milk, sometimes with the addition of cereal gruels and porridges if the nutrition is not sufficiently maintained. Meats should be avoided.

During convalescence from scarlatinal nephritis the greatest precautions must be taken against undue exercise and chilling of the body. The patient should not be allowed to leave the bed until the albuminuria has become very slight, if not entirely absent, and while in bed should always be warmly covered to favor continued action of the skin. When allowed to be out of bed he should be warmly clad, and the transit to the outside air made only on dry, warm, and still days, if the reason permits.

If possible, temporary sojourn in some warm, salubrious region is to be sought.

Respiratory Complications and Sequels.—These are less common than some other complicating conditions. Bronchopneumonia and croupous pneumonia are not infrequent sequels. The former is most likely to develop at the end of grave septic cases. Serous and purulent pleuritic effusions of an inflammatory nature are not uncommon. The treatment of any of them is that of the same condition due to other causes.

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CHAPTER XIII

ERYTHEMA INFECTIOSUM

Henry L. K. Shaw

Synonyms.—In studying the literature on this disease one is greatly impressed with the lack of agreement as to just what constitutes its distinctive features. That it differs in many essential points from the three classical exanthemata, scarlet fever, measles and German measles, is agreed by all, but the clinical descriptions of this eruptive outcast vary in different countries. It seems not improbable that eruptive disorders described under the name of roseola infantum, Oerliche Rötheln, megalerythema epidemicum, grossflechen, exanthema variable, erythema infantum febrile, epidemischer Kinderrotlauf, fourth disease, fifth disease, pseudorubella, rubella scarlatinosa, exanthem subitum, etc., should be grouped under the term "erythema infectiosum."

Definition.—Erythema infectiosum is a febrile exanthem occurring chiefly in young children. It has definite periods of incubation, invasion and eruption. The constitutional symptoms are slight and the eruption forms the characteristic feature. It is apparently very feebly communicable, has an unknown etiology and is without complications or sequelæ.

History.—The earliest description of this disease appears in the German literature. Tschamer in 1886, under the name "Oerliche Rötheln," gave a very clear account of the clinical history and characteristic eruption but felt he was dealing with an abortive type of German measles. Escherich, ten years later, reported a number of similar cases which he had observed in Gratz and made the first claim that it was a disease *sui generis* and was not identical with German measles. Schmidt, one of his assistants, gave a very exhaustive description of this disease in 1899 based on a study of 121 cases. Strickler of Giessen in the same year described a similar epidemic and was the first to employ the term "erythema infectiosum" which has since been generally accepted by the German writers.

Weber reported an epidemic which occurred in Switzerland in 1916 which he was convinced corresponded in all its essential symptoms to the cases described as erythema infectiosum. Dukes in England described several epidemics to which he applied the term "fourth disease" but its clinical entity as such has not been generally accepted. Many years before Filatow of Russia reported a similar epidemic. There is great similarity between the accounts of these two authors and there is possibly some relation between fourth disease and erythema infectiosum.

In this country a small epidemic occurred in a village near Buffalo which was studied by an experienced dermatologist and a competent pediatrician who were both convinced that the disease was not scarlet fever, measles or German measles and claimed that it corresponded in every important detail with the course and description of erythema infectiosum.

It is very possible that epidemics reported as atypical forms of the common exanthemata should be included under this diagnosis. The cases described by Zahorsky of St. Louis in 1910 and 1913, under the name "roseola infantum," might be included under the classification of erythema infectiosum.

Westcott of Philadelphia reported a series of cases with almost identical eruption and symptoms which he called pseudorubella. The 30 cases observed by Levy in Detroit in 1921 possessed many similarities. Veeder and Hempleman described a somewhat similar epidemic in St. Louis in 1921 and proposed the name "exanthem subitum." This past year Greenthal reported a similar epidemic occurring at Ann Arbor, Michigan, and Goldbloom observed 5 cases of a similar type in Montreal.

The nomenclature would be simplified and the atmosphere cleared if all of these cases could be classified under the diagnosis of erythema infectiosum.

Etiology.—The specific agent, mode of transmission and life of the contagion is unknown. The age most frequently affected is between nine months and six years. The period of incubation appeared to be between five and fifteen days in 6 definite cases reported by Coerper.

Epidemiology.—Erythema infectiosum does not occur frequently and it is therefore difficult to study its epidemiology. It is only feebly communicable and the susceptibility to it is not very general. A number of Weber's cases were recognized in an orphan asylum where only two or 3 cases developed each week. Coerper had in Barmen 18 cases, of which 3 were in a children's home of 32 children and 6 in a "rachitis station" among 25 children from one to four years of age. An attack of scarlet fever, measles or German measles affords no immunity against erythema infectiosum. It is probable that one attack gives immunity for life. The reported epidemics were most frequent in the spring and early summer. It is not known how long the disease is contagious. Both sexes are equally affected.

Symptoms.—In many cases the subjective symptoms are conspicuous by their absence. There may be more or less fever, malaise, coated tongue, loss of appetite, nervous irritability for from two to four days. When the general condition of the patient seems to improve, the skin eruption appears. In other cases there are no prodromes and the rash is the first symptom observed.

The rash is macular, reddish in color with a bluish undertone and disappears on pressure. On the trunk the macules are morbilliform and the center is paler and appears sunken. On the face the rash may coalesce and become confluent, giving the cheeks the appearance of a facial erysipelas, although in many cases the face is not affected. The eruption does not itch or feel hot to the touch. It spreads rather rapidly over the trunk and towards the periphery, the hands and feet being the last portions of the body to be affected. On the arms and legs the center of the maculopapular spots fades out, but the periphery remains, giving the arms and legs a lacelike mottling. The rash fades rapidly from the face and trunk but more slowly from the arms and legs. There is no eruption seen in the mouth or on the fauces and the superficial glands are not enlarged as in rubella. There is no coryza, conjunctivitis or cough as in measles. Veeder and Hempleman confirmed the blood findings of Weber, who found in every case a marked leukopenia with an increase of lymphocytes and a decrease of the polynuclear leukocytes. Most of the more recent writers have emphasized this characteristic blood picture. Blood cultures have been negative.

Prophylaxis.—It is impossible to prevent its spread as so little is known of the source and character of the contagion, its mode of transmission and the length of the period of invasion. For this reason it is unnecessary to deprive children of their education by keeping them out of school. No isolation is necessary as the communicability seems to be so slight as to be negligible. The most important point is the question of diagnosis, that is, not to confuse it with the other exanthems. The expense involved in the maintenance of quarantine, the services of a trained nurse, etc., are considerable and a great injustice is wrought to both the parents and the patient when a wrong diagnosis is made and the child unnecessarily placed in seclusion.

Treatment.—Before the appearance of the rash, the symptoms usually point to some slight digestive disorder. Rest in bed, a restricted diet and the use of some mild laxative are indicated. The temperature should be reduced by hydrotherapy and if necessary by small doses of aconite. When the rash appears, relief may be obtained by sponging the skin with a solution of bicarbonate of soda, 1 dram to the pint, a saturated solution of boric acid, or a weak solution of alcohol and water (1:10). A simple dusting powder may also be used.

The cases should be kept isolated in view of the fact that there is an element of contagion present and it is prudent to keep the child in quarantine until the eruption has disappeared.

CHAPTER XIV

INFLUENZA

William H. Smith

Pfeiffer's publication of his discovery of the influenza bacillus in 1893 led to the hope that a definite etiology for influenza, as for typhoid and tuberculosis, had been found. The influenza bacillus is accepted generally to-day as the cause of epidemic influenza, but there is no such clear-cut, definite importance attached to its presence in secretions as in the case of the gonococcus, tubercle, or typhoid bacillus.

The literature from 1895 is filled with reports of the isolation of the influenza bacillus from the sputum, or at postmortem in cases of measles, scarlet fever, diphtheria, and tuberculosis (Leiner, Wohlwill, Jehle, and others). Similar, if not identical, organisms have been found in conjunctivitis and whooping-cough. The writer has repeatedly isolated influenza bacilli from the sputum in cases of chronic bronchitis and bronchiectasis; and has found that these bacilli persist for years in the bronchial secretion; and that they may be present in practically pure culture at the time of an acute exacerbation.

The prevalence of the influenza bacillus, so widespread, and associated with so many diseases, especially with the acute exanthemata, has led, on the part of some, to skepticism as to the actual pathogenic power of these bacilli. In patients with disease, clinically influenza, the absence of the influenza bacillus has tended to increase this skepticism. Curschmann in such an epidemic reported the presence of the pneumococcus in 46 out of 49 cases. The presence of the pneumococcus, streptococcus, streptococcus mucosus, Micrococcus catarrhalis, and staphylococcus, has been reported in similar acute infections resembling influenza.

The presence of hemophilic bacilli, similar to the influenza bacillus, with slight variations, as described by Bordet in whooping-cough, and recently by Cohen in cerebrospinal meningitis, has raised the question as to whether subvarieties of the influenza bacillus might not exist. The pseudo-influenza bacillus described by Pfeiffer is, according to Jochmann, judging from the present evidence, but a modified form of the influenza bacillus.

The uncertainty of the bacteriologist is paralleled by the indefiniteness of the clinician. Any acute cold is called influenza by some clinicians; others, dwelling on the widespread occurrence of the bacillus in other diseases, even when they find the influenza bacillus in the secretion of the suspected case, question whether these bacilli may not be saprophytes, and hesitate to call the disease influenza. A third group takes the fixed stand that where the influenza bacillus is there is influenza.

Pfeiffer's dictum that the bacilli were not found in the blood is becoming more and more questioned at the present time, because of the ever-increasing number of cases of septicemia, pyemia, endocarditis, arthritis, and meningitis reported by accurate observers with bacteriological data. Horder's case of endocarditis in which the influenza bacillus was isolated from the blood four times during an interval of six weeks is a remarkable one; the influenza bacilli were isolated from the valve in pure culture at autopsy. The results obtained by Ghedini in cultivating this organism from the blood are surprising, when, in 28 patients with influenza, the influenza bacillus was isolated 18 times, or 64 per cent; and from 14 spleen punctures recovered 8 times, or 57 per cent. These observations need further confirmation. He insists that the blood culture must be taken during the fever period. The future may show that the influenza bacillus will be found to produce many acute and chronic conditions now little suspected. Blood cultures should be more generally employed by clinicians to determine if some of the fevers of unknown origin may not be due to an infection with the influenza bacillus.

Admitting the indefinite bacteriological and shifting clinical position, but accepting the influenza bacillus as the cause of epidemic influenza, let us consider its treatment.

The pandemic of 1918 and 1919, with its residual legacy of 1920, left much to be desired in the way of the causative factor. Owing to the World War, the widely scattered medical forces, and the large number of individuals affected with the disease, the opportunity for concentrated study was impossible. The etiological factor has not been determined with accuracy. There are those who believe the influenza bacillus was causative, while others are in doubt. If one reads the literature, world-wide, since the cessation of the epidemic, one is again confronted with the fact that no specific treatment seemed to be of any avail. There is no unanimity of opinion as to the value of the use of vaccines as a prophylactic measure or in the treatment of the disease. While claim is made for the therapeutic value of convalescent sera by some, others found it of no avail. One has but to glance over the large list of drugs used, the claims made for one in Italy, another in France and still others in America, to realize how impotent we really were in the treatment of the disease during this pandemic.

It is uncertain to-day what the future therapy of influenza will be.

This uncertainty must exist as long as there is such indefiniteness in regard to the infecting agent. Whether treatment will emerge along the lines of vaccines, serum therapy or chemotherapy is at present on the lap of the gods.

Prophylaxis.—The source of infection lies chiefly in the nasal and bronchial secretions. A study of the last pandemic seemed to show that new districts became infected when visited by persons with the disease; that mild unrecognized cases might infect; that infection followed direct lines of communication.

The pandemic of 1918-1919 leaves us uncertain as to the infecting agent. This uncertainty makes prophylactic treatment by the use of vaccines questionable. Favorable reports in the literature of the use of vaccines can be matched by unfavorable ones. The evidence of previous epidemics of influenza seems to have been brought out clearly in the recent pandemic, namely, that the source of infection seemed to lie chiefly in the nasal and bronchial secretions, that direct contact favored infection, as did the crowding which occurred in transports and training camps in the World War. The more rapid means of transportation also favored its spread.

Any attempt to isolate all cases of influenza during a pandemic is impossible; it is likewise impossible to restrict travel or enforce quarantine for a disease usually so mild, of short duration and low mortality. Absence of a direct means of treatment, which in the future may be offered by a serum therapy, makes it impossible to provide actual prophylaxis. The difficulty of any prophylactic means is increased because of the short incubation and easy communicability of the disease. The presence of bacilli, in interepidemic periods, in so many possible carriers, as shown by Holt, Lord, and others, renders it even more difficult, especially as the prevalence of these cases is not generally recognized by physicians. Certain suggestions may be made. When possible, persons with influenza should be isolated. Sputum and nasal secretions should be collected on gauze and burned. In sneezing and coughing infected persons should hold gauze or a handkerchief before the face. The clothing and dishes used by the patient should be washed separately. Elderly persons and children, when the disease is epidemic, should be kept from contact with any case, however mild. Unnecessary attendance at crowded gatherings should be discouraged. Fatigue and overexposure should be guarded against. It is possible that hexamethylenamin (0.56 gm.), 7½ gr. three times a day, may have a prophylactic value. Quinin and oil of eucalyptol have also been recommended. Patients with chronic cough whose sputum contains influenza bacilli should take especial care to destroy their sputum. Rooms occupied recently by patients with influenza should be disinfected with formaldehyd.[1]

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[1] The value of the gauze mask in prophylaxis is still in doubt.—Editor.

TREATMENT

Specific Treatment

Judged from our present knowledge the disease is a toxemia; it may occasionally be a septicemia or pyemia. It is generally conceded that one attack confers but slight, if any, immunity. At present we have insufficient data in regard to any direct treatment with vaccines, antitoxin, or immune sera, although Cantani and Latapie obtained sera having certain protective properties. Isolated cases have been reported where vaccines were used, but the results are not uniform.

Flexner has reported that a serum has been obtained from goats which had been inoculated for a long time and repeatedly with virulent cultures of the influenza bacillus. This serum had been found an efficient therapeutic agent for experimental influenzal meningitis in monkeys. This discovery leads us to hope in the future for the serum treatment of influenza, especially for those cases of meningitis due to this bacillus.

The striking thing about the epidemic of 1918-1919 was the great prevalence of pneumonia as a complication. If one studied the lungs at postmortem, one was impressed with the impossibility of any specific treatment in the presence of the pneumonic complication, because of the presence in the consolidated areas of streptococci, staphylococci, pneumococci, as well as mixtures of these organisms. If any specific treatment appears in the future, it must meet the stage of invasion to prevent the pulmonary edema and hemorrhage which favored the bacterial growth in the lungs. If recognized early, pneumonia due to Type 1 pneumococcus may be treated by the appropriate serum.

Since the infecting agent is not proved, it would seem fair to doubt the value of any direct, specific treatment at present, based either upon a vaccine made from a single organism or from a combination of several. There seems from the evidence to be a question as to the value of pooled immune sera. An expert knowledge of serology is certainly necessary where any attempt by direct serum treatment is to be made.

General Treatment

One has only to read the treatment employed during the epidemics of the sixteenth and seventeenth centuries as detailed in *The Annals of Influenza,* published by the Sydenham Society, where bleeding, purging, blistering, and emetics were extensively used, to realize that the tendency of the disease is to recovery. In spite of the treatment of those times the mortality was low. In the pandemic of 1918-1919 the mortality was high. This high mortality was due to the prevalence of pneumonia as a complication, to the frequency of pulmonary edema and hemorrhage. The pneumonia was especially fatal in pregnant women.

The onset of the disease is usually sudden, with chill, or chilly sensations, occasionally with delirium or coma. The temperature rises suddenly to 101° or 102°, or even higher; the proportional rise of pulse is frequently much less. The respiratory rate was exceedingly high in the recent epidemic. Coincident with the onset of the disease irritation of the nose, pharynx, larynx, or trachea may be noticed, with at times acute inflammation of the tonsils. The headache may be extreme, frequently frontal or orbital, or there may be, from the toxins, a meningeal irritation simulating meningitis, as in certain of the other acute infections. The soreness and lameness in the muscles of the back and thighs may be very great, the prostration marked. In the recent epidemic the tendency to hemorrhage was very great. At times hemorrhage into the abdominal muscles simulated an acute abdominal condition such as an acute appendix or an acute gall-bladder. Until one had seen at postmortem the large amount of blood-clot in the abdominal muscles, and learned to recognize the clinical condition, one found it difficult to exclude some acute intra-abdominal infection. The cyanosis which accompanied the recent infection was most marked and a striking feature was the irritating cough, at times non-productive, at times associated with bloody mucoid, or, where a pneumonia had developed, with bloody mucopurulent sputum. Within from forty-eight to seventy-two hours the temperature may be normal and the patient comfortable. The transition from health to disease in influenza is frequently very rapid, as may be the recovery in patients whose condition at onset was most grave.

If seen at the beginning of the disease the patient should be put to bed, as there is no way of estimating the amount of toxin present, or the resistance of the individual patient, and experience has shown that patients thus treated suffered less from complications and slow convalescence than did those who tried to work and keep about.

When practicable the patient should be isolated, the sputum and nasal secretion collected on gauze and burned. If the bowels have not moved a mild purge like sodium phosphate (2.8 to 3.8 gm.) 45 to 60 gr., or a small dose of hydrargyri chloridium mite (0.032 to 0.065 gm.), gr. ½ to 1, followed by some mild saline, may be given. A warm bath may be taken, while hot drinks like lemonade, milk, or whisky may be given to favor perspiration and to dilute toxins.

For the pain and discomfort some of the antipyretics like acetphenetidin (0.65 gm.), gr. 10, with caffein (0.065 gm), gr. 1, can be ordered, repeated in an hour. Variation in the size or frequency of the dose must be determined by the patient's condition and the judgment of the physician. Aspirin (0.65 gm.), gr. 10, every hour for three or four doses, may be given, or sodium salicylate or quinin. Acetanilid, because of its depressing effect, is seldom needed in this disease and should only be used where the susceptibility of the patient to this drug is known beforehand. In the absence of any direct antitoxic treatment the object is to relieve the headache, backache, hyperesthesia, and general discomfort produced by the fever and toxins, by diluting these toxins, and to obtain comfort for the patient with the least depressing drug. If, at the beginning of the attack, there is much cough which is irritating, hard and non-productive, some sedative in addition to the antipyretic should be used, such as codein (0.015 to 0.030 gm.) gr. 1/4 to 1/2. Small doses of pulvis ipecacuanhæ et opii (0.5 gm.), gr. 7 1/2, will be of value. At times for the severity of the pain morphia must be used.

Diet.—The patient should be fed according to his digestive capacity. If there is much renal irritation present, meat and meat soups should be used sparingly. Water in abundance should be taken to dilute toxins.

Fever.—The fever in the usual, acute, uncomplicated case of influenza is of short duration and seldom needs treatment. Hyperpyrexia may occur, but even this is seldom long continued. Cold baths for reduction of fever in this disease should not be used. The patient should be kept in bed, or, at least, in his room, until the morning and evening temperatures are practically normal. Usually in uncomplicated cases, at the end of three or four days the acute toxic manifestations have subsided, the temperature has reached normal by lysis, and the patient has become comfortable. Relapse more severe than the original attack may occur, or debility and prostration with protracted convalescence may follow the mildest case. In those patients previously debilitated, or in whom the nervous system is unstable, too early a return to customary occupation should be forbidden, as in this type of patient relapse is more prone to occur and neurasthenic symptoms or delay in convalescence is more probable.

TREATMENT OF TYPES

Dependent upon the localization of toxins certain types in influenza have been described. Leichtenstern's classification is as follows:

I. The purely toxic variety.
    A. The simple influenza fever.
    B. The nervous form of influenza.
II. The toxic inflammatory.
    A. The catarrhal respiratory.
    B. The gastro-intestinal variety.

Osler's classification is the more usual one:

I. Respiratory.
II. Gastro-intestinal.
III. Nervous.
IV. Febrile.

It is impossible to maintain, in certain cases, any clear-cut separation into types, as frequently the various forms are combined or merged into each other. A study of 847 cases [2] of influenza recorded at the Massachusetts General Hospital showed the majority to be of the respiratory type, while a large number of these patients at entrance so simulated typhoid that they were placed on enteric precautions. In certain epidemics a tendency to hemorrhage has been observed, but this type is less common. Hemorrhage from mucous membranes and into various organs was frequent in the 1918-1919 epidemic.

Respiratory Type.—The discomfort in the pharynx and tonsils, which is present in some cases, is usually relieved by the simple antipyretic treatment. For the engorged larynx and trachea, where it is possible, steam inhalations are of value. Compound tincture of benzoin, 3 or 4 c.c., may be added to 1 or 2 liters of hot water and the steam inhaled. The steam atomizer with an oil spray may be used.

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Albolene	(30 c.c.)	1℥
Menthol		
Eucalyptol	āā (0.65),	gr. 10

The Acme atomizer is a good one. Special attention should be paid to the possible infection of the sinuses and middle ears. The use of warm normal salt solution with a Birmingham douche, by keeping the mucosa clean, is said to lessen this danger. When infection of the sinuses occurs, steam inhalations or the use of adrenalin spray (1: 5,000) or a 1 or 2 per cent solution of cocain may favor natural drainage by shrinkage of the engorged nasal mucous membrane. Morphia may be needed for the pain, or operative interference necessary. Paracentesis should be performed early if the middle ears become infected, thereby lessening the danger of mastoid involvement and sinus thrombosis.

Bronchitis.—This may be circumscribed, unilateral, or very extensive, involving the smallest bronchioles. The sputum may be abundant and at times bloody. In the acute stage a small dose of a sedative like codein (0.015 gm.), gr. ¼, may be used. With much secretion sedatives should be used with caution. Later, if the secretion is abundant and difficult to raise, ammonium chlorid (0.32 gm.), gr. 5, may be taken with some hot drink every three or four hours. In the more chronic bronchitis, which often follows the attack, potassium iodid (0.32 gm.), gr. 5, in milk three or four times a day is recommended. Change of climate is advisable for patients in whom the bronchitis is protracted, if the condition of the patient otherwise permits. For the paroxysmal cough occurring in influenza quinin is said to be of value.

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[2] The diagnosis of these cases was in the main clinical rather than bacteriological.

Gastro-intestinal Type.—Symptoms from the gastro-intestinal tract may arise during an attack of influenza. These symptoms may be the only manifestation of the disease, or, as is more usual, they may appear in association with symptoms from the respiratory tract. These symptoms vary from simple dyspepsia, gastric irritation with nausea and vomiting, intestinal irritation with colic and diarrhea, to those in the rarer cases where blood may be vomited or bloody diarrhea may occur. Reiss, in analyzing the cards in the German Collective Investigation of the epidemic of influenza in 1889 and 1890, found, of 3,231 cards submitted, catarrh of the stomach was present in 610, or 18.9 per cent; catarrh of the stomach and intestines in 502, or 15.5 per cent; catarrh of the intestines alone in 233, or 7.2 per cent. Loss of appetite, vomiting, and diarrhea were the more common manifestations of the effect of the toxins on the gastro-intestinal tract, occurring in from 32 to 34 per cent of the cases. Pain was a rare manifestation, present in from 4 to 5 per cent. The percentage of cases bleeding from the stomach or intestines was 5.3 per cent. The condition of the gastro-intestinal tract varies from a mild gastro-enteritis to extensive engorgement of the mucosa with hemorrhage. Swelling of the Peyer's patches and mesenteric glands has been observed. Ulceration in the jejunum has been reported by Kuskow. The influenza bacillus was isolated from the pus of an appendix abscess by Adrian; and Fisch and Hill have reported a case of purulent peritonitis with isolation of the influenza bacillus in pure culture. During an epidemic of influenza great care should be taken not to attribute to the influenza toxins abdominal pain really due to an acute inflammation of the appendix.

The treatment of the gastro-intestinal manifestations of influenza, whether occurring alone or associated with the respiratory or nervous form, must be symptomatic. If any food is retained, milk, or milk and vichy, koumiss, albumin water, or thin gruels may be taken. If the nausea persists, rectal feeding may be necessary. Hot salt solution enemata, or seepage, if the bowel is not too irritable, may be of benefit. The dilution of toxins should be attempted by having the patient drink an abundance of water, and, if this is impossible, salt solution should be used subcutaneously. The excretion of this fluid should be favored through the skin and kidneys. Brandy and shaved ice, or champagne, in small amounts taken frequently may relieve the vomiting. Bismuth subnitrate (1.9 to 2.9 gm.), gr. 30 to 45, may be given every six or eight hours. Some of these cases are relieved by acetphenetidin, or other simple antipyretics. The symptoms are, fortunately, usually of short duration, but vomiting may persist and much loss of flesh occur. This type of the disease was rare in the cases at the Massachusetts General Hospital. Cholecystitis, due to the influenza bacillus, has been reported by Laubheimer, Heyrovsky, and Knina, four cases in all, where the bacillus has been isolated. Karewski and Ruheman each report a case of liver abscess in influenza, but the bacteriology is indefinite. Neutralization of toxins by dilution, favoring elimination through the skin and kidneys, symptomatic treatment of the nausea with careful feeding with the use of bismuth or some allied drug represent, at present, our means of treatment. Counterirritation has been advised; in certain cases opium or morphia must be used for the pain or frequent bowel movements. If acidosis is present, alkalis may be of value.

Nervous Type.—In addition to the headache, delirium, the occasional case beginning with coma, the restlessness and insomnia, all manifestations of the toxin on the nervous system, cases have been reported of hemiplegia, myelitis, encephalitis, paralysis resembling Landry's, where organic change has occurred. The literature is very extensive of the cases with neuralgia and multiple neuritis, together with the cases of exhaustion psychoses and occasional mania. From Leichtenstern's collection of cases it is seen that scarcely any portion of the nervous system has escaped injury from the influenza bacillus or its toxin. The tendency of the usual mild manifestations due to toxemia is to subside under the ordinary treatment with antipyretics, warm baths, and the usual measures suggested to dilute toxins; abundant fluid intake, favoring perspiration, salt solution by rectum or under the skin. Drugs or drug treatment must be applied for the relief of symptoms. When organic lesions, such as encephalitis or myelitis, are present, there can be no specific treatment in the light of our present knowledge. It is to be hoped that in the future some specific treatment like an immune serum will be found which not only will neutralize the toxins produced by this bacillus, but will prevent the extensive organic changes so frequently reported as having occurred in the nervous system, due to the destructive process of the influenza bacillus or its toxins. The persistent neuralgias, exhaustion psychoses, acute manias, tend to recover and do not differ from similar conditions seen less frequently after other acute infections like typhoid or pneumonia. The underlying debility must be recognized and tonic baths, with other hydrotherapeutic measures, employed. Massage, forced feeding, in certain cases a modified rest cure, must be insisted on. Quinin in large doses is said to act well for the persistent neuralgias. If facial neuralgia persists the possibility of antrum disease must be considered. Liquor potassii arsenitis (0.24 c.c.) minims iv, well diluted after meals, increasing the dose gradually, is recommended, as is also strychnia in some form for the debility and general weakened condition. Drugs for sleeplessness, which is often persistent, must be used, but should be used only in connection with other measures, the aim of which is to build up the general condition of the patient. When pain is absent sulphonethylmethane (1 gm.), 15 gr., or chloralamid may be of value. Certain of the American neurologists think the importance of the influenza toxins on the nervous system has been overestimated. The underlying neurotic disposition, in many of the patients suffering after an attack of influenza from nervous manifestations, is recognized by several writers.

COMPLICATIONS

Pneumonia.—This is one of the most dangerous complications of influenza. Its frequency varies in different epidemics and in various localities. It is usually a bronchopneumonia or lobular pneumonia. Mixed infections with the streptococcus and pneumococcus are common. Lobar pneumonia, when a complication, is probably due to the pneumococcus. The recognition of the bronchopneumonia in influenza is frequently difficult, at times impossible. Exacerbation of symptoms, with rise of temperature, pulse, or respiration, should suggest it. The areas of consolidation are frequently so small that dulness is lacking and bronchial expiration absent. Attention has been called to the frequency with which these foci may be multiple.

In 11 fatal cases studied by the writer where influenza bacilli were present in the exudate, in culture, and in sections of the pneumonic foci, in 1 case four lobes showed foci of consolidation, three lobes 3 times, two lobes once, and one lobe 6 times. The right upper lobe was involved in five cases.

The possibility of confusing such cases with tuberculosis must be mentioned. The diagnosis in interepidemic periods may be made by the sputum examination; the sputum may be mucopurulent, purulent, or at times blood-tinged, and will frequently show the presence of the influenza bacilli in large numbers alone or in association with the streptococcus or pneumococcus.

The sputum should be typed to determine the presence or absence of pneumococcus Type 1. If this is present and the recognition is early, direct serum treatment may be employed.

When extension into the lung has occurred, supporting measures must be pushed, nutrition kept at a maximum and rest, as near absolute as possible, must be maintained.

The fluid intake should be abundant, 1,500 to 2,000 c.c. daily for an adult. If the pneumonia is associated with abundant expectoration, sedatives such as codeia or morphia must be used in small doses. Expectoration should be favored by the use of ammonium chlorid or aromatic spirits of ammonia if there is extensive bronchitis.

If the heart shows signs of weakness, caffein sodiobenzoate, hypodermically, 0.1 gm. or 0.2 gm., may be given and repeated. Some preparation of digitalis, either the tincture, or digitan, or a pill made of the standardized leaf will be of value. Elderly people stand digitalis well in this type of pneumonia. Intravenous or subcutaneous injections of sterile salt solution may be employed.

As the disease is frequently of long duration, attention must be paid to obtaining sufficient sleep. Paroxysmal cough is apt to strain the abdominal muscles and a tight binder often gives comfort and favors the expulsion of the secretion. The use of alcohol in the form of whisky or champagne may be left to the choice of the individual physician. When secretion is not excessive or when easily raised, morphia may be used. Trional (0.65 gm.), gr. 10, may be all that is needed. Where the heart's action is good and kidney secretion free, liquids should be given freely. The disease terminates usually by lysis. Recrudescence may occur and typhoid or tuberculosis be simulated. The signs of consolidation may persist in exceptional cases for weeks. If pleuritic pain is present it may be controlled by a tight swathe, by hot or cold applications, or, in certain cases, morphia will be needed. The possibility of pneumothorax from the subpleural perforation of a bronchopneumonia patch, localized abscess, gangrene, or empyema, as reported by Mosler, Fürbinger, Kundrath, Pfeiffer, and Rhyner, must be remembered in this type of pneumonia. Bronchiectasis may be a sequel. The mortality of influenza pneumonia is variously stated at from 17 per cent (the German Collective Report) to 43 per cent (by Kranhalls). Ghedini has recently called attention to the pleural effusions after this disease. Davis reports in one case of influenza pneumonia treated with influenzal vaccine 500,000,000, that there were chill, rise of temperature, and local reaction.

In one patient with chronic bronchiectasis, exacerbation, and influenzal pneumonia, observed by the writer, injections of vaccine were followed by hemoptysis.

Cardiocirculatory Complications.—The acute cardiac failure following influenza leaves little opportunity for direct treatment. The subcutaneous injection of camphor, ether, alcohol must be tried. The heart suffers in two directions from the action of the influenza bacillus: the effect of the toxins producing irritability and myocardial insufficiency, and the more rare effect on the endocardium and pericardium. For the irregularity dependent upon nervous change, rest, at first with strychnia (0.0016 gm.), gr. 1/40, every six or eight hours may be valuable. The patient must be considered as well as his heart, and careful feeding and general tonic treatment carried out. If there is myocardial weakness with dilatation and limitation of the field of cardiac response, tincture of digitalis should be used. Spiritus etheris compositus, atropin, and strophanthus have each been recommended. Krehl, in speaking of the diseases of the heart occurring after influenza, is inclined to think that in most cases the cardiac disturbances are chiefly to be explained by an increase in the already existing cardiac affection and by the influence of the general damage to the nervous system and the general health. The pathology of cardiac change in influenza is less well understood than is this change after most of the acute infections. The recent accurate observations on influenzal endocarditis, with the reported cases of Spät, Saathoff, Horder, and Smith, should attract attention to the possibility of the influenza bacillus being more frequently a cause of endocarditis than has been considered in the past. At present the treatment must be symptomatic. Horder suggests, in another case, he would inoculate the patient with a dead culture of the organism, hoping that by a process of vaccination the increased resistance of the patient might combat the infection. The case of septicemia, secondary to bronchopneumonia, reported by Madison, where influenza bacilli were isolated from the blood, recovered after an illness of sixty-eight days. Thursfield has recently reported two cases of septicemia, one secondary to an attack of influenza, the second following a phlebitis. In both patients the influenza bacilli were isolated from the blood. Recovery occurred in both cases.

Meningitis.—One of the rarer manifestations, formerly of bacteriological and pathological interest, has, during the past few years, become of interest clinically. It is now known from bacteriological proof that meningitis due to influenza bacilli is sufficiently widespread to suggest that in the past cases have been overlooked. The attention of the clinician was called to this by Cohoe and Adams. Cohoe, in 1909, collected 26 cases from the literature where the bacteriological data were fairly trustworthy. In the article by Davis 40 cases were collected, 5 cases being observed in Chicago in a little over a year. Since this paper other cases have been reported in America, France, and England. Recently Wollstein has stated that 8 cases have come under her personal observation. Cohoe states the mortality of his 26 collected cases as 85 per cent. Flexner records that all but 6 of the 58 cases up to the present reported have died. The increasing number of these cases calls the attention of the clinician to the necessity of their recognition.

Treatment.—Batten records one case where urotropin was used with recovery of the acute condition. In two other cases treated by influenza vaccine, 25,000,000 and 12,500,000 in one case and 2,500,000 in the other, both died. Lumbar puncture should be employed for diagnosis. Relief of symptoms, particularly severe headache, has followed its use in influenzal meningitis.

Rarer Complications.—The treatment of the occasional thrombosis or phlebitis occurring in this affection must be symptomatic. Nephritis, toxic in type, secondary to influenza, is a rare complication, seldom occurring in infants. The tendency is to recovery. During the acute stage the patient should be confined to bed and kept between blankets so that a more uniform temperature may be obtained. His diet should be bland. A mild diuretic like mistura ferri et ammonii acetatis (3.7 c.c.), 1 dram, every six or eight hours, may be all that is needed. Occasionally the nephritis becomes chronic. Fatal cases have been reported. Affection of the joints with pus formation due to the influenza bacillus has been reported by Dudgeon and Adams, Weil, Slawyk, and Fraser. While usually part of a pyemia, in Fraser's case, where the knee was involved, incision was followed by recovery.

Chronic Influenza, Bronchiectasis.—Pfeiffer first called attention to the persistence of the influenza bacillus in the sputum after the acute attack. Leichtenstern reports 2 cases, simulating tuberculosis, followed for two years, with postmortem examination excluding tuberculosis. Lord reported, in 1902, 18 cases of chronic infection with the influenza bacillus.

In 2 cases followed by the writer for two years, influenza bacilli were constantly cultivated from the sputum. Postmortem examinations in both showed diffuse bronchiectasis and pneumonitis.

The cases usually have chronic cough, worse in winter, with abundant purulent or mucopurulent sputum. They are subject to acute exacerbations or even bronchopneumonia; one patient has had three such attacks in five years. Hemoptysis may occur, and the question of phthisis is often raised; indeed, in some cases this mistake has been made. They are subject to asthmatic attacks, and, unless the underlying bronchiectasic condition is recognized, sedatives will do harm, when expectorants or mild emetics, by favoring emptying of the cavities, will benefit. This condition is found in youth and in early adult life as well as in middle age. Repeated sputum examinations may be necessary for diagnosis, for frequently a shower of influenza bacilli will appear suddenly, and isolation in pure culture is simplified. Several of these patients have had their sputum examined repeatedly for tubercle bacilli with negative results. They have not reacted to tuberculin.

It is very important that these cases should be recognized, and during acute exacerbations of the disease, or bronchopneumonia attacks, blood cultures should be made to see if the influenza bacilli may not be isolated.

Treatment.—A 24-hour estimate of the amount of secretion should be made, as it gives an index of the degree of damage present. Patients should be taught to drain their cavities; oftentimes if hot drinks are sipped before rising, while dressing, or before meals, attacks of coughing are prevented and frequently the sputum is raised more easily and the exhaustion resulting from the exertion of coughing is minimized. This is important especially in elderly people in whom the tendency to emphysema is marked or cardiac insufficiency probable. A mild saline cathartic should be taken to keep the intestinal tract clean, for it is impossible to prevent swallowing some of the secretion, which is oftentimes excessive. One patient was relieved of a chronic diarrhea by the simple procedures mentioned above. Expectorants, such as potassium iodid or ammonium chlorid, should be used to favor secretion; codein and heroin should be withdrawn. If stasis in these cavities occurs and the sputum or breath becomes foul, oil of eucalyptus (0.12 to 0.18 c.c.), minims 2 or 3, on sugar two or three times a day may be found of value. The hemoptysis requires no treatment. The asthmatic attacks are relieved by expectorants.

For the acute exacerbations with fever, malaise, headache, and, not infrequently, bronchopneumonia, the treatment as outlined for those conditions should be used. As many of these patients are practically free from cough in the summer months, in the winter they may find comfort in a warm climate; the tendency is, however, to recurrence wherever they are. Boggs, and Madison, and Beck have called attention to these chronic bronchitis cases with bronchiectasis, with influenza bacilli in their sputum.

Surgery at present offers little relief for the condition. The difficulty of localization is extreme, the cavities are frequently bilateral and multiple. The X-ray plates are frequently unsatisfactory because of the associated thickened pleura. Lobectomy may be considered in selected cases.

Convalescence

In no disease may an attack apparently so mild be followed by such debility, prostration, and frequent insomnia. In most of the cases, after the acute attack is over, restoration to health is rapid and complete. Where debility and prostration persist, long absence from work must be urged, the appetite catered to, forced feeding insisted upon. Massage, arsenic, iron, or quinin, hydrotherapy, all in certain cases will be needed. Each individual case must be studied and appropriately treated for the underlying condition of debility, asthenia. Where the cough persists, selected cases will benefit by climatic change. This should not be urged, however, unless equally good food and home comforts can be obtained. Patients with organic change in heart, lungs, or kidneys should be particularly guarded in convalescence from influenza.

SUMMARY

Epidemic influenza may be due to the influenza bacillus. The frequent presence of this bacillus in acute infections other than influenza minimizes its importance. Frequent so-called epidemics of influenza are due to other organisms. Influenza bacillus is rarely present in the blood in culture. Influenza meningitis and endocarditis are rare complications.

Prophylaxis.—Vaccines are of doubtful value since the infecting agent is not proved. Secretions from nose and throat dangerous. Face should be protected by gauze in coughing and sneezing. Sputum burned.

Specific Treatment.—No antitoxin; vaccines of limited use. Value of pooled convalescent serum still in doubt. No direct treatment by immune serum.

General Treatment.—Isolation where possible. Care of secretions. Antipyretics. Acetphenetidin, caffein, quinin, sodium salicylate, aspirin, acetanilid, codein, pulvis ipecacuanhæ et opii, digitalis, caffein sodiobenzoate.

Diet.—According to the digestive capacity. Fluids to dilute toxins.

Fever.—Usually short duration, no specific treatment. Avoid cold baths.

Respiratory.—Inhalations, steam, or oil sprays. Antipyretics. Codein for cough. Adrenalin spray for sinus infection or cocain solution. Early paracentesis for middle-ear involvement. Ammonium chlorid, potassium iodid for subacute bronchitis; quinin for spasmodic cough.

Gastro-intestinal.—Alkalis, if acidosis is present. Liquids, soft solid diet. Favor elimination through skin and kidneys. Salt solution enemata. Brandy, shaved ice, champagne. Antipyretics, bismuth or allied drug. Opium.

Nervous.—Warm baths, salt solution. Antipyretics. Later massage, tonic baths. Hydrotherapy, liquor potassii arsenitis, strychnia, sulphonethylmethane, chloralamid.

Complications—*Pneumonia.*—Type sputum. Direct serum treatment in presence of pneumococcus Type 1. Maximum nutrition, alcohol, strychnia, caffein, digitalis, sterile salt solution. Favor elimination and expectoration. Morphia, sulphonethylmethane. Frequent slow convalescence. Lysis.

Cardiocirculatory.—Camphor, ether, caffein, alcohol, strychnia, digitalis, belladonna, strophanthus, spiritus etheris compositus.

Meningitis.—Possibly hexamethylenamine. Lumbar puncture. Symptomatic.

Septicemia; Pyemia.—Symptomatic. Alcohol, possible influenza vaccines.

Rarer Complications.—*Phlebitis; thrombosis.* Symptomatic. *Nephritis.* Bed, bland diet, mild diuretics.

Arthritis.—Incision, if pus present.

Chronic Influenza; Bronchiectasis.—Favor expectoration, warm drinks, ammonium chlorid, potassium iodid, saline cathartics. Avoid sedatives where there is much secretion. Oil of eucalyptus. Climate. Surgery offers but little. Lobectomy may be advised in the selected case. Diagnosis difficult, cavities frequently multiple.

Convalescence.—Treat patient. Tonics, rest, absence from work, massage. Iron, arsenic, quinin, hydrotherapy, climatic change.

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CHAPTER XV

ACUTE ARTHRITIS, INCLUDING RHEUMATIC FEVER

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PATHOGENESIS OF ARTHRITIS

Progress toward a satisfactory understanding of the pathogenesis of arthritis has been retarded by the relative obscurity of the etiology of some types, and, in other forms whose etiology has been better known, by ignorance of the mechanical factors which lead to the lodgment and growth of bacteria in joints and other structures of the body. Modifications in our views as to the presence of bacteria in the blood in disease have had an important influence on our conceptions of the mechanism of production of arthritis. Whereas formerly the presence of bacteria in the blood was regarded as of serious significance, indicating usually a terminal event in the course of sepsis, we now know that in diseases such as typhoid fever and pneumonia bacteriemia occurs regularly, and that in other diseases such as the complications of gonococcal infection, in which the organisms were formerly thought to be confined to the original site of infection, a demonstrable though intermittent bacteriemia occurs. By studying a series of infections of the same etiology which exhibit decreasing degrees of virulence, it is readily possible to find instances in which cultural examination of metastatic lesions in joints demonstrates the presence of viable organisms which must have reached the joint by way of the blood, but whose presence in transit in the blood excited no symptoms suggestive of bacteriemia. In such cases the joint lesion can no longer be explained on the theory that it is due to toxins formed at a distant point and acting in some unexplained way on the tissues of a particular joint. The course of the lesion thus initiated will depend on the viability and vigor of growth of the bacteria in the embolic focus on the one hand, and on the degree and nature of reaction of the tissues of the joint on the other. The bacterial embolus reaches some portion of the periarticular structure and a minute focus is formed either in the more superficial portions of the joint, or deeper in the capsule, or in the tissue underlying the synovia. In the latter case the layers of cells of the synovialis become swollen, and at the point of greatest damage desquamation of the altered cells of the synovial surface occurs. This irritation may cause a rapid increase in synovial secretion with resulting distention of the joint. The effusion may be sterile, or it may contain the invading organism if the latter has passed from the subsynovial focus through the damaged tissues of the synovialis. If the bacterial embolus lies at a point more distant from the synovial surface, there may be but little or no involvement of the synovialis, the lesion presenting the clinical features of a periarthritis. The relatively avascular joint offers conditions of oxygen tension and of protection from the antibacterial forces of the host which differ from those in the blood, and, in so far as these conditions favor either the growth or the destruction of the organism, they will influence the course of the arthritis.

Improved bacteriologic methods have yielded much new information as to the sources of the bacteria whose entrance into the blood-stream is first evidenced by embolic phenomena. The bacteriemia may be due to, and a part of, the primary disease, as in pneumonia or epidemic meningitis, or it may arise through the invasion of the host by secondary infecting organisms, such as the streptococcus or staphylococcus, as in variola. In the acute arthritis of focal infection, the primary disease in tonsil or elsewhere may occasion no remark, the first evidence of invasion being the local disturbance at the site of the embolism.

In considering acute arthritis it is important to bear in mind that in an infection of a joint by an organism there are several factors which determine the character of the resulting lesion.

There are certain peculiarities of the organisms themselves which determine the type of lesion, experience teaching that one organism is likely in the majority of instances to produce suppurative lesions while another usually gives rise to non-suppurative processes. Thus, of a number of joint lesions arising in streptococcal sepsis we expect a larger proportion to become suppurative than of a like number of joint lesions developing in gonococcal sepsis. At the same time we know that suppurative arthritis, and even suppurative myositis, may exceptionally be caused by the gonococcus, and that, on the other hand, arthritis due to streptococcal infection often subsides promptly without formation of pus. Our conception of the clinical picture of each form of arthritis is based on what usually happens, but here as in all other medical problems it is important to remember the exceptions as well as the rule. The behavior of an organism is affected no doubt not only by its own average characteristics and powers of growth in a host of given species, but also by peculiarities of food supply, and tissue reactions afforded by the individual host of the species. Varying degrees of susceptibility to infection on the part of different individuals is a fact universally recognized in medicine. This variable susceptibility to the attack of an invading organism not only determines whether invasion shall occur at all, but must also exert an influence on the type of lesion produced after successful invasion has taken place. The activity of the resistant forces of the host, the degree of protection afforded to the invader by the different tissues in which it finds itself, and the condition of the tissues with respect to previous injury and daily trauma of use, will thus influence the subsequent course of the local contest between invader and host, and so determine the type of lesion, whether it is to be transient or chronic, rapidly healing or suppurative.

Thus there are a number of factors which enter into the formation of the clinical picture of acute arthritis, whether produced by various organisms, or by the same organism in persons of varying general or local susceptibility. In general the type of organism seems to be more important than individual susceptibility of the human host in determining the course of the arthritis, and so from the clinical type of the arthritis one may draw some, though perhaps limited, deductions as to the probable bacterial etiology of the infection.

Other associated lesions and diseases, either preceding or accompanying the arthritis, such as scarlet fever, angina, gonorrhea, or sepsis, frequently furnish the clew to the probable nature of the invading organism. In other instances the source of the infection is local, small, and often less evident, so that a more careful examination and consideration of all the possible sources of infection are necessary before the real cause can be determined. Arthritis arising from such local infections is often recurrent, and through repeated attacks the joints sustain more permanent injury, the arthritis then passing into one of the several forms of chronic joint disease. But such cases are often seen during the first attack, and then call for a differential diagnosis from the other possible types of acute arthritis. In these cases, even more than in the arthritis associated with acute infectious diseases, a correct etiologic diagnosis is important to the patient; for if the source of his infection, such as an abscess in the tonsil, can be found and removed, he may be spared the discomfort of subsequent attacks and the dangers of prolonged or permanent disability of the chronic forms of joint disease.

Bacteriologic examination of the evident sources of infection, and of the synovial effusion when this can be obtained, affords valuable information as to the cause and also as to the prognosis and treatment of the joints involved. But a lack of facilities for extensive bacteriologic studies by no means precludes the possibility of a successful search for the cause of acute arthritis, even in the large group of patients in whom other characteristic symptoms of clinically recognizable infectious diseases are absent. The studies of recent years on the causes of arthritis, while greatly assisted by newer and more incisive methods of bacteriologic study, have been aided to an equally large extent by improvement of clinical methods of examination, such as the X-ray, and by the renewed recognition of the self-evident fact that every patient should be submitted to a painstaking and minute physical survey.

The old surgical maxim that it is the closed process from which absorption of infection is most likely to take place has been again brought to the fore. Equally important is the recognition of the fact that the site of the initial infection need not be a large one. Bacteria may pass from very small and unnoticed foci into the blood-stream and produce multiple arthritis as well as other lesions in distant parts of the body.

CLASSIFICATION OF ACUTE ARTHRITIS

While there is still much to learn of the pathogenesis of acute arthritis, a convenient working classification based on etiology may be formulated even in the imperfect state of our present knowledge.

The large majority of cases of acute arthritis fall into one of the following three large groups:

1. Acute arthritis associated with the infectious diseases and caused (*a*) by the organism responsible for the primary disease, as in pneumonia, epidemic meningitis, and streptococcal sepsis; and (*b*) by secondary invading organisms, such as the staphylococcus in variola.
2. Acute arthritis associated with local primary infections, in which the source of the infection may be clearly evident from coincident clinical symptoms, or so obscure that the only symptoms are those of the joint lesions.
3. Acute arthritis of rheumatic fever.

Whether the arthritis will heal, leaving functionally intact joints, or whether there will remain permanent anatomic changes which will be increased by recurrences of the acute process in the joints will depend on the combination of circumstances in the individual case, including the nature of the infecting organism and the opportunities for reinfection, together with the many factors which modify the reaction of the joint tissues to the injury.

Other forms of acute arthritis less commonly encountered are those due to external trauma with or without perforation of the joint, the arthritis of gout, the arthritis met with in the hemorrhagic diseases, scurvy, and serum disease, and the arthropathies associated with nervous diseases, such as tabes, in which the onset may be sudden and the joint present the appearance of an infectious arthritis. The arthritis occurring with the purpuras is associated with fever and other symptoms suggestive of an acute infectious process, and further studies may place these forms of joint disease close to rheumatic fever, with which they have many points in common.

ACUTE ARTHRITIS COMPLICATING THE INFECTIOUS DISEASES

In the acute infectious diseases of known etiology in which the specific organism is present in the blood, arthritis occurs as an occasional complication.

The pneumococcus, which usually localizes in the lung and gives to the infection the well-known clinical characteristics which we recognize as lobar pneumonia may also invade the joints, and pneumococcal arthritis is an occasional complication of pneumonia, or of pneumococcal sepsis in which pulmonary symptoms may be absent. Likewise, acute arthritis is occasionally seen in epidemic meningitis, and the meningococcus can be demonstrated in the purulent exudate. In Malta fever arthritis is frequent, and rarely it is seen in typhoid fever. In these the suppurative or non-suppurative lesions in joints may be accompanied by metastases elsewhere—in serous membranes, bones, lymph-nodes—or the joint inflammation may be the only apparent gross lesion.

In erysipelas and in streptococcal sepsis the joints are invaded with somewhat greater frequency. In tuberculosis, besides the usual chronic tuberculous arthritis, there occurs more rarely an acute arthritis often of the larger joints, such as the knee or ankle, which in the first days of its appearance suggests the arthritis of the acute infections. Some of the acute arthritis seen in tuberculosis is no doubt due to secondary bacterial infection, but in some instances tubercle bacilli have been demonstrated in the joint lesions.

In syphilis an arthritis in which acute exacerbations occur is sometimes seen, particularly in the subjects of congenital syphilis.

The exanthemata are often complicated by secondary invasions of pyogenic bacteria, which localize in joints, serous membranes, bones, and lymph-nodes. It is, of course, possible that the etiologic infectious agents of the exanthemata, as well as the pyogenic bacteria, may invade the joints and share in the pathogenesis of arthritis, but of this we have no direct knowledge. Numerous instances of secondary arthritis are noted in scarlet fever, in which streptococcal bacteriemia with metastases in joints is frequent. Severe attacks of measles also may be complicated by secondary pyogenic infections involving bones and joints.

Streptococcal infections of the throat and nasal passages, which in recent years have occurred in epidemics in most parts of this country, arising in some instances from infected milk supplies, in other instances apparently by contact, have exhibited a remarkable number of complications, among which have been instances of arthritis. As in other streptococcal infections, many of these joint lesions heal after a short period of activity, without the formation of purulent arthritis, but a few present severe suppuration requiring drainage. Some patients who exhibit complications, such as sinusitis, otitis, or peritonsillar abscess, later, after the acute symptoms in the throat have subsided, suffer from a new invasion, with multiple arthritis, which may be recurrent. Such instances constitute the more acute forms of arthritis which result from a type of focal infection to be referred to later. The occurrence of arthritis and other metastases in some persons, and the absence of lesions beyond the local infection of the mucous membranes in others, all of whom are subjects of infection by the same or closely allied organisms in the same epidemic, again emphasize the importance of individual variation in susceptibility and resistance to infection.

Treatment.—The treatment of this type of acute arthritis is largely symptomatic. In many instances the arthritis is the only evidence that bacteria have been present in the blood-stream. The nature of the primary disease will usually give a clew to the etiology of the arthritis.

In addition to general supportive treatment suited to the disease in which the arthritis occurs, measures must be taken to relieve pain in the affected joints. Hot applications are valuable. Immobilization, partial or complete, depending on the degree and site of joint involvement, should be accomplished by means of pillows, sandbags, bandages, or splints. Whatever the method employed, it should never interfere with the daily observation of the affected joint. When effusion occurs, it is often wise to aspirate the joint; if the effusion is large, the removal of fluid gives great relief to the patient. The early detection of purulent arthritis and the institution of drainage may be the means of saving the joint from irreparable damage, while also removing from the patient one source of intoxication. It must be remembered, however, that even in the arthritis due to invasion by pyogenic organisms the joints may heal without suppuration.

There are instances of severe streptococcal infection in scarlet fever, in which the patients become progressively more and more toxic with multiple suppurating joints, but this extreme picture is not the rule, the majority of cases of streptococcal arthritis healing without the necessity of surgical interference.

In the diagnosis and subsequent care of this type of acute arthritis, the possibility of acute osteomyelitis must always be borne in mind. Osteomyelitis adjacent to a joint may simulate arthritis, and sometimes arthritis and osteomyelitis occur together. In addition to the data from physical examination, repeated roentgenograms are of great value in arriving at the diagnosis.

Meningococcal arthritis, which occasionally is seen following epidemic meningitis, has been successfully treated by aspiration of the joint and injection of antimeningococcic serum.

Syphilitic arthritis usually yields promptly to antisyphilitic treatment, including iodids and mercury.

ACUTE ARTHRITIS ASSOCIATED WITH LOCAL INFECTIONS

In general the acute arthritis arising from localized infections does not differ in the mechanism of its production from the arthritis occurring in certain of the acute infectious diseases in which bacteriemia is regularly present.

While the arthritis is likely to occupy the center of the clinical picture, the general symptoms of infection may vary greatly in degree. The local lesion which formed the infection atrium may be clearly evident in one case; in another it may be entirely hidden. Gonococcal arthritis affords a good example of the range in the degree of the arthritis and of the symptoms of general infection. In one patient multiple arthritis may suddenly appear during a chronic gonococcal infection, with scarcely any fever or general symptoms of infection; in another patient, the arthritis may be accompanied by symptoms of severe sepsis, high fever, and a readily demonstrable gonococcemia. In the latter form the arthritis might be regarded as properly belonging in the previously described group, which includes cases arising in the course of acute general infections, but in its more common form the prominent features of gonococcal arthritis are the arthritis and the local genital infection.

But in addition to the evident local infections, such as abscesses, suppurating wounds, or gonococcal infections which have long been recognized as portals of entrance into the blood-stream of organisms which localize in joints, the studies of recent years have demonstrated sources of infection entirely hidden from casual examination, giving rise to no local disturbance sufficient to suggest their presence. The discovery that from such relatively small and hidden sites bacteria can pass into the blood-stream and lodge in distant structures of the body such as those of the joints, eyes, muscles, or tendon sheaths, and there set up lesions affording the first evidence that infection is present, is of the greatest importance in the diagnosis and treatment of these disabling affections, and has facilitated the understanding of the entire subject of lesions of joints, muscles, nerves, and special organs of the body.

During the cold and wet seasons a strikingly large number of the patients in the medical wards of hospitals, particularly of the large centers of population, are found to be suffering from some form of arthritis. Some of these present on admission the clinical picture of rheumatic fever, and the subsequent course confirms the diagnosis. Others who on entrance show symptoms of rheumatic fever, after a few days fail to exhibit the migratory character of joint lesions, or in other aspects early lead the physician to question whether after all they may not be suffering from some other form of arthritis.

Rheumatic fever itself presents many variations in its course, and there is no one absolutely diagnostic symptom. Nevertheless, cases of rheumatic fever present a rather characteristic complex, to which many of these other cases do not conform. The latter constitute to a large extent the acute arthritis group consecutive to focal infection. Occasionally acute arthritis conforming in almost all essentials to rheumatic fever is met with following local infections of the extremities, such even as a subungual streptococcal infection.

While rheumatic fever is a very common disease, there seems to be no doubt that many cases diagnosed as rheumatic fever are in reality types of acute multiple arthritis arising from chronic infections in alveolar abscesses, chronic tonsillar abscesses, prostatic infections, non-venereal as well as gonococcal, the acute infection developing in the patients after prolonged exposure to debilitating influences, such as cold, wet, poor food, or severe exertion, without sufficient opportunity for rest and recuperation.

Cutaneous lesions, erythematous and nodal, are seen with the arthritis arising from focal infection as well as with that of rheumatic fever. Acute or recurrent tonsillar infection is found associated with erythema nodosum and arthritis, and the same streptococcus has been isolated from all three sites. In ulcerative endocarditis of the subacute or chronic type due to Streptococcus viridans, subcutaneous and intracutaneous tender nodes appear, especially in the finger tips, and they may be accompanied by acute transient arthritis. In all these forms of joint diseases it would seem more important to emphasize the element of bacterial embolism occurring in the course of a bacterial invasion of the blood, now with one, now with another organism, rather than attempt to ascribe all clinically similar lesions to one specific organism.

The conditions which determine the type of lesion, whether in joint, skin, or muscle, whether slight and temporary or chronic with pronounced inflammatory edema or frankly suppurative, are probably many and concern on the one hand the general type of species of the invading organism, as well as its finer peculiarities and growth requirements, and on the other hand the degree of resistance of the tissue of the host, both local and general. It is the combination of these circumstances, which may be expressed in relative terms of the invasive power of the organism and of the resistance of the host, that in any given case determines the type of lesion produced. It is not surprising, therefore, that clinically similar lesions may be found in a variety of infections. At the same time it must be remembered that under approximately the same circumstances a given organism is likely to behave in a more or less constant manner, a fact which insures a fairly constant clinical picture in some infections, but does not prevent exceptions when the complex of circumstances varies, and does not prevent variations in the severity or types of complications during different epidemics.

Treatment.—The first consideration in the treatment of acute arthritis from whatever cause is the comfort and safety of the patient. Relative or absolute rest, the protection of inflamed joints by bandages, cotton pads, or by various degrees of fixation by splints, the giving of analgesics when pain is severe, appropriate diet depending on the degree of the coincident general infection, and appropriate surgical treatment when excessive effusion or suppuration occurs, are measures which are to be employed in acute arthritis without regard to its cause.

Every patient suffering from arthritis should receive a thorough examination. This should include exploration of all possible sources of infection—the sinuses by direct examination and by transillumination and roentgenograms; the teeth by direct examination and roentgenograms followed by expert dental consultation; the tonsils, particularly those which are more or less buried by adhesions and scar tissue, by careful exploration; the prostate in men and the pelvis in women—and other routine physical examinations and investigations of the blood and urine. To many, these suggestions will seem unnecessary; to others they will appear to impose an excessive labor without hope of reward commensurate with the effort involved.

The temporary relief obtained by symptomatic treatment should not prevent further efforts to arrive at an etiologic diagnosis, for apart from the desirability of thoroughness of examination in general, such a search is not infrequently rewarded by the discovery of some condition which permits of the application of more specific, and perhaps rapidly curative, measures.

It may be urged that because the treatment of acute arthritis is largely symptomatic, whether the arthritis occurs in rheumatic fever or in other forms of infection, the question of the exact etiology is more academic than practical. This position is not tenable, both because it is subversive of true progress in medicine and because by taking it the physician misses many opportunities for service to the patient.

When patients are thus carefully examined and relieved of the chronic infections, wherever found, the results in hastened cure of the arthritis and in the freedom from recurrence are often remarkable. By no means all patients proceed to rapid and complete recovery, but the proportion who respond to treatment directed against the cause of the illness, when this can be found, renders a faithful trial of these measures well worth while in all cases.

Some of the failures of treatment based on this search for the source of the infection have been due to the incompleteness of the examination. Multiple foci of infection are surprisingly frequent in such patients. It is not sufficient to stop the search on the finding and removing of one infected area; the examination should be continued until no further infections can be demonstrated.

Treatment of Gonococcal Arthritis.—For treatment of Gonococcal Arthritis see Chapter LVI.

ACUTE ARTICULAR RHEUMATISM (RHEUMATIC FEVER)

Confusion in the use of the term "rheumatism" has arisen through lack of knowledge of the etiology of the various types of arthritis, as well as through the further misuse of an already vaguely defined term to describe almost any condition presenting symptoms suggestive of the pain or disability popularly recognized as attendant on arthritis. With increasing knowledge of the pathogenesis of arthritis it has been possible gradually to define groups of arthritis in accordance with their several microbic and other causes, so that there is at present no further excuse for continuing the loose use of the word "rheumatism."

Following the usage of those who have given the best thought to the subject, this discussion confines the term "rheumatism" to the disease known also as rheumatic fever, or acute articular rheumatism, a malady which the studies of years stamp as a fairly well-defined clinical entity. It has been urged in the interest of accuracy that a word so badly abused as "rheumatism" might well be discarded altogether, but until there is a general agreement as to the etiology of the disease the term "rheumatism" used in this restricted sense will give good service.

Notwithstanding the almost universal recognition of rheumatism as a specific disease, until its etiology has been admitted as finally and conclusively proved a brief and yet satisfying definition is difficult or impossible. In the more common form seen in young adults, the sudden onset often following exposure, with fever, acute polyarthritis, with swelling, redness, and pain, involving large and also, perhaps to a less extent, the small joints, the subsidence of arthritis in joints first developed with rapid invasion of new joints, the sweating, the rapidly developing anemia, the frequent complications of endocarditis and pericarditis, and the tendency to relapse with renewal of the symptom complex are quite characteristic. A preceding or initial pharyngitis or tonsillitis is frequent.

Variations from this type, in which the arthritis is much less marked, the febrile symptoms less severe or the course less stormy but more chronic, are often noted. In children the disease may pursue a smoldering course with occasional slightly marked febrile attacks and anemia, and, while joint symptoms are scarcely recognizable, injury to heart valves progresses. Here the rheumatic nodes along tendon sheaths, particularly in the palms and about joints, described by Cheadle, may give a clew to the nature of the illness. These fibrous nodes are not peculiar to rheumatism, however, being found in other infections having a chronic course and low virulence. Chorea also is so frequently associated with rheumatism, either antecedent to or following the attack, as to lead to the view that the two diseases may have a common cause.

Etiology

That rheumatism is an infectious disease seems evident from the symptoms and course, which in general resemble those of other diseases of known infectious etiology. The occurrence of unusual numbers of cases of rheumatism in epidemic fashion, as described by a number of writers, also suggests an infectious cause, as does to a less degree the incidence of the disease in several members of a family which may indicate some inherited susceptibility.

A number of views have been held as to the nature of the infectious agent in rheumatism. Some have held that it is multiple, including the staphylococci and streptococci found in other infections, but which exhibit modified degrees of virulence. The theory of a "modified pyemia" expresses somewhat the same view. Poynton and Paine isolated a small diplococcus from cases of rheumatism, which they called "Diplococcus rheumaticus." In cultures it occurs in pairs or short chains. Previous investigators had isolated similar diplococci, and the occurrence of the diplococcus in the blood, joints, and subcutaneous nodes in rheumatism has been confirmed by subsequent studies of Poynton and Paine and their associates, and by others.

Inoculated into animals such as rabbits or monkeys, this diplococcus has produced joint and cardiac lesions resembling those of rheumatism. There seems but little question that the Diplococcus rheumaticus is a cause of rheumatism, but to prove that it is *the* cause is a matter of more difficulty. With improved cultural methods, particularly the use of tall dextrose agar tubes in which varying degrees of oxygen tension were afforded, Rosenow was able to obtain the diplococcus from the blood or joint fluid in 16 of 18 cases of rheumatism cultured. Cultures must be made early in the disease, usually within the first two or three days, in order to obtain organisms. On the one hand, the production of joint and cardiac lesions in animals by inoculations of the diplococcus does not, of course, afford final proof of its causal relation to the disease, and, on the other hand, the fact that joint and cardiac lesions follow the inoculation of animals with various strains of streptococci or pneumococci need not by any means disqualify the experimentation with the Diplococcus rheumaticus as a link in the chain of etiologic evidence. Nor does the occasional finding of other organisms, such as bacilli, staphylococci, or streptococci, in cultures from patients with rheumatism present a valid argument for a multiple etiology; for, with the increasing frequency and improved technic with which cultures from blood and tissue are being made, it has become evident that in many diseases bacterial invasion of the blood by organisms clearly not etiologically related to them is a common occurrence.

While it is advisable still to maintain an open mind as to the etiology of rheumatism, the evidence is growing that the Diplococcus or Streptococcus rheumaticus of Poynton and Paine must be seriously considered as a cause of the disease.

Prophylaxis

The low immediate mortality and the frequency of recurrences of rheumatism afford opportunity for the employment of measures to prevent subsequent attacks, and the serious consequences of the complications, especially those involving the heart valves, impose an added responsibility upon the physician to do all in his power to avoid renewed activity of the infection, which if continued will sooner or later lead to invalidism.

In the case of those who have suffered from previous rheumatism, severe exposure to cold or wet must be avoided. The lesser degrees of exposure, which usually produce no noticeable effects in the average child, may be sufficient to precipitate an attack in one who has recently suffered from the disease. Attempts to guard the child from exposure should not, however, lead to undue confinement; abundant opportunity should be allowed for outdoor exercise. Cold, damp, poorly ventilated and poorly lighted houses are often associated with other insanitary conditions which help to depress the physical condition of the occupants, and favor the development of diseases of which rheumatism is one. The social worker renders efficient service in helping to remedy the bad conditions of housing, ignorance as to proper diet, and neglect of cleanliness which are common among the poor of both large and small centers of population.

The effect of sudden changes of temperature is demonstrated in the frequency of rheumatism and other forms of acute arthritis among butchers and others whose work necessitates their entrance many times a day into cooling rooms. A change of occupation may be necessary in such cases to insure freedom from subsequent attacks.

Children and adults who are subject to rheumatism or are convalescent from an attack may be sent with benefit to a warmer climate during the inclement months of the year.

Removal of Sources of Infection

A considerable proportion of cases of rheumatism are preceded by tonsillitis, and in recurrent forms of arthritis the tonsils are often chronically enlarged and infected, with enlargement of the lumph-nodes of the neck. Removal of the tonsils has been followed in a considerable proportion of cases by cessation of attacks of arthritis. There seems to be no doubt that in some of these instances of successful prophylaxis by tonsillectomy the arthritis has resembled more closely the multiple arthritis of focal infection than that of typical rheumatic fever. In other instances tonsillectomy seems to have prevented the recurrence of undoubted rheumatic fever. It has already been pointed out, however, that while a series of typical cases of rheumatic fever resemble each other so closely as to leave no doubt of the propriety of regarding the disease as a clinical entity, there is frequently difficulty in determining whether in the individual case the disease is rheumatism or an arthritis due to another infection. There is much to recommend the theory that acute arthritis is caused by the invasion of joints by a number of possible invading organisms of varying degrees of invasive power in hosts of varying degrees of resistance, and that in a certain proportion of cases which go to make up the type recognized as rheumatic fever the invader is an organism of relatively constant degree of invasive power, which leads to a fairly constant type of joint lesion.

Whether or not we concede that the tonsil may be the residence of the cause of rheumatism between attacks, and thus afford a portal of entry when for any reason the resistance of the patient is lowered, there is still another reason why attention to diseased tonsils is of benefit in preventing rheumatism. Persons who suffer from chronic tonsillar infection, whether children or adults, often show the effects of the chronic intoxication by evident disturbances of various functions of the body, apart from the development of definite metastatic lesions. When such persons are relieved of their infections, improvement of general health follows, and, in so far as general good health and nutrition can assist in increasing resistance to disease, they are in a better position to withstand other infections. In this way, the removal of diseased tonsils, or other foci of infection, may have an additional prophylactic value in the treatment of rheumatism.

It has been urged that the present agitation in regard to the tonsil is a fad, that many unnecessary tonsillectomies are being done, and that the removal of the tonsils often fails to prevent recurrences of rheumatism. It must be admitted that tonsillectomy, even when thoroughly performed, does not offer certainty of freedom from rheumatism, but experience has shown that when the tonsils are diseased their removal is advisable, especially if there is a history of acute inflammation, unless there is some very clear contra-indication.

Other possible local sources of infection, such as adenoids in children and the sinuses and teeth in older persons, should be sought for, and so far as possible should be removed. The need for these measures is more evident in the recurrent arthritis due to infections other than that of rheumatic fever, but the sufferer from rheumatism should also be allowed to profit by relief from chronic local lesions, which no doubt often contribute to the depression of his resistance to infection and make him more susceptible to the infection of rheumatism.

TREATMENT

The important objects in the treatment of rheumatism are the comfort of the patient and the prevention so far as possible of complications involving heart valves, both of which are best attained by prolonged rest in bed.

The sufferer from rheumatic fever has before him the prospect of a number of days or perhaps weeks of illness, during which in addition to the discomfort occasioned by fever and other symptoms of infection, he will suffer severe pain in many joints. It is well at the outset to recognize the possibility of a somewhat protracted illness and to arrange for details of the sick room which will add to his comfort, and prevent unnecessary suffering. The sick room should be well ventilated, and if possible have an exposure which allows of the entrance of direct sunlight at some time during the day. The bed should be narrow, not more than three-quarter size, with firm springs and a smooth mattress. The usual type of bed is too low, and if the higher hospital type of bed is not available, blocks may be placed under the ordinary bed after removing the rollers. The use of a higher bed facilitates the frequent changes of the bedding and clothes of the patient, thus greatly lightening the labors of the nurse and lessening the suffering of the patient entailed by the necessary manipulations.

The bed covering, which should be light, should be prevented from making pressure on inflamed joints. Wooden barrel hoops cut in half, crossed, and wrapped with bandage, make very convenient supports. The use of blankets next to the patient is much less insisted on now than in former years. The prevention of chill following the sweats can be attained by frequent changes of sheets and gown, without undue disturbance of the patient if a competent nurse is in charge. The gown of the patient should be open at the back to allow of easy removal.

Treatment of Joints.—The rheumatic joint is the seat of an acute inflammation, excessively painful while it lasts, but likely to subside within a few days. While in part spontaneous, most of the pain results from motion, and immobilization of the affected joints affords a measure of relief to the patient often as great as that attained by analgesic drugs. Cotton wrapping surrounded by a bandage not too tight may be adequate, but more often the inclusion of a light, well-padded splint in the outer turns of the bandage is necessary to obtain immobilization sufficient to relieve pain. Cardboard is a familiar and easily obtainable splint material which often affords sufficient fixation to the smaller joints. The splint must be rigid enough to allow of the relaxation of involuntary muscular tension. Plaster of Paris casts have been sometimes advised, but the temporary character of the arthritis seems hardly to warrant the increased manipulations necessary in their application. The larger joints to which splints cannot be so readily applied may be immobilized with pillows or sandbags.

Pain in joints not relieved by immobilization may sometimes be relieved by hot compresses. In other cases cold applications are more grateful to the patient. The use of blisters and cautery is occasionally advised, but in general it would seem wiser to employ other measures, including analgesic drugs, before resorting to these remedies, which may leave the patient with an additional source of irritation to trouble him long after the arthritis has passed on to other joints.

Counterirritants such as liniments may be applied gently. When oil of wintergreen is not offensive to the patient it may be used, and, in so far as salicylates exercise a favorable effect on rheumatism, it serves a double purpose in acting as a local counterirritant, and later, after absorption, on the disease itself.

Diet.—The appetite during the height of a severe attack of rheumatism is often very poor, so that it may be difficult to persuade the patient to take even small amounts of nourishment. It is important to meet the loss of energy entailed by prolonged fever, and to maintain nutrition in order to increase resistance to the infection. The lesson we have learned in recent years of the advantages of fuller diet in the treatment of typhoid might well be applied to the treatment of rheumatism, particularly as regards the giving of an increased amount of carbohydrates to meet the wastage entailed by prolonged high fever.

Milk is given freely unless distasteful to the patient, or one of the many milk products may be substituted. Cereals, including rice, bread, and gruels, will serve to raise the caloric value of the diet. Cream and butter and an occasional egg, or custard, may be allowed. A plentiful supply of fluids, which may include lemonade, fruit juices, and the alkaline mineral waters, should be given.

The diet should be increased upon convalescence, and may then include with benefit moderate amounts of meat.

It is important to avoid associating in the mind of the patient, particularly a child, the taking of medicine with the taking of food, and so far as possible the two should be given at different times. This is especially true in rheumatism where salicylates are likely to be given over long periods of time.

Drugs—*Salicylates.*—The drug most widely used in the treatment of rheumatism is salicylic acid. The action of salicylic acid and its salts in rheumatic fever has been and still is a matter of controversy. On the one hand are those who believe that salicylic acid acts more efficiently in the arthritis of rheumatic fever than in other forms of arthritis and that its efficacy in relieving symptoms entitles it to be regarded as specific in the disease. Others maintain that its apparently specific effects are confined to the relief of pain, and that, so far as a direct effect upon the infection itself goes, patients receiving salicylic acid require on the average as long a period for recovery as do those not so treated. The analgesic action of salicylates in arthritis is certainly not limited to that of rheumatic fever, for in cases of gonococcal arthritis, the lesions of which are in many respects similar to those of rheumatism, the relief of pain by salicylate is pronounced. Indeed salicylates are valuable in the relief of pain arising from a variety of causes. The arthritis of rheumatic fever is typically an evanescent process usually persisting in a joint for a few hours or days only, whether treated or not. When to the relief of pain following the use of salicylates there is added the disappearance of inflammation from the affected joints, the temptation is obviously great to attribute both results to the remedial agent. The weak point in the argument for specificity appears when new joints become involved while the patient is still receiving the same dose of salicylates that supposedly brought about the cure of the joints first involved. If we compare the effects of salicylates on other forms of arthritis with those on the arthritis of rheumatic fever, having in mind the distinction between symptomatic analgesic effects and those of a more specific nature, the results in the two classes of arthritis appear to differ for the most part only when the arthritis of non-rheumatic origin departs from the type of arthritis usually seen in rheumatic fever. Whether or not we accept the conception of rheumatic fever as an infection by the Diplococcus rheumaticus, it is, however, a fact that the arthritis of rheumatic fever shows a remarkable uniformity in its course in the joints, and that the number of joints in which suppurative lesions or even permanent non-suppurative changes occur is extremely small as compared with the arthritis caused by other organisms such as the gonococcus or streptococcus. In so far as the arthritis due to the latter is of slight degree and rapid in healing, such favorable outcome might be attributed to salicylates as well as in rheumatic fever, where evanescent lesions are more constantly seen. Clinical experience seems to indicate, therefore, that the favorable action of salicylates is attributable in large part to their analgesic action, and that the response to salicylates in a given joint lesion depends on the nature and severity of the lesion, which in turn is determined by the infecting organism and the general and local resistance of the patient. However, in view of the fact that the joint lesions in which relief of pain is accomplished by salicylates predominate in rheumatic fever and are less regularly seen in arthritis of other types, the action of salicylates in rheumatic fever may perhaps be thought of as "specific," though not in the same sense as the word is used in reference to the action of quinin against the malarial plasmodium, or of the arsenic compounds against spirochetes.

Sodium Salicylate.—The most commonly used preparation of salicylic acid is sodium salicylate. Opinions differ as to the optimal dose of sodium salicylate in rheumatism. Some advise large doses, approaching the toxic dose of 150 to 200 gr. a day; others believe that much smaller doses are equally efficient. The middle course is probably advisable, allowing 60 to 90 gr. per day during the first two or three days, or until the analgesic action of the drug is obtained. This dose would be attained by giving to an adult 10 to 15 gr. every two or three hours for six doses during the waking hours. After two or three days, the dose is decreased to 10 gr. four times a day. Unusual circumstances or individual susceptibility may require an increase or decrease of this dose. There is much individual variation in the degree of gastric disturbance occasioned by salicylates, some persons tolerating large doses without complaint, and others manifesting symptoms of gastric irritation, of burning in the epigastrium, and even pain after relatively small doses.

Sodium salicylate is preferably given in solution, well diluted with water, and not in capsules. Alkalis, such as sodium bicarbonate, should be given in at least twice the dose of the salicylate; they serve the double purpose of increasing gastric tolerance of the drug and of helping to maintain the alkalinity of the tissues. Milk or other suitable food taken just before the salicylate assists in preventing irritation of the stomach.

Delirium has been observed following large doses of salicylates, and minor symptoms such as tinnitus are seen even after smaller doses. While sodium salicylate alone can undoubtedly produce such symptoms, it seems probable that many of the complications, such as erythemas and perhaps some of the instances of delirium have been caused by the disease and not by the drug.

Other salts of salicylic acid, such as strontium salicylate, have been proposed as substitutes for sodium salicylate, but recent pharmacologic studies cast a doubt as to their superiority.

Derivatives of Salicylic Acid.—A number of compounds of salicylic acid have been produced which are said to be superior to sodium salicylate in that they produce less gastric irritation, or have a less disagreeable taste. The nausea and vomiting which occasionally follow their ingestion have been thought to be cerebral in origin.

Acetyl salicylic acid (aspirin) is widely used. It has the advantage of yielding the salicyl radical in large amount only in alkaline solution and hence passes through the acid stomach without being broken up to more than a slight degree. It should not be given in immediate company with alkalis. In small doses it may be administered in capsules, but when larger doses, 30 to 60 gr. a day, are employed, it is preferably given in a powder.

Phenyl salicylate (salol) also is broken up only in alkaline solution, and is thus less irritating to the stomach than is sodium salicylate. Care must be used, however, in giving large doses over long periods on account of the possible toxic action of the phenol set free.

Among other salicyl derivatives of the acetyl salicylic acid type are diaspirin (succinyl disalicylic acid), diplosal (salicylo-salicylic acid), and novaspirin (methylene citryl salicylic acid). Corresponding to the methyl salicylate (oil of wintergreen) type are ethyl salicylate and mesotan (methyl oxymethyl salicylate).[1] These and other synthetic products possess physical and chemical qualities in addition to their novelty which in special circumstances may recommend them in place of sodium salicylate and oil of wintergreen, but the action of the salicyl radical, for the sake of which they are for the most part given in rheumatism, is not different from the salicyl radical of sodium salicylate. While these products are given in doses containing equivalent amounts of salicylic acid, many experienced clinicians observe no constant advantage in their action as regards lessened gastric irritation over that of sodium salicylate when it is given with sufficient bicarbonate of soda.

Alkalis.—Throughout the attack of rheumatism the patient should receive sufficient alkalis to prevent the development of acidosis. This may be accomplished by giving sodium bicarbonate and small doses of potassium bicarbonate or, combined with them, the salts of organic acids, such as the citrates. Sodium citrate may be administered in lemonade. Efficient alkalization is determined by the maintenance of an alkaline reaction in the urine.

The alkaline treatment recommended by some clinicians consists thus of thorough alkalization, and it is contended by some that cardiac complications are less frequent under this management than under treatment by salicylates.

Other Analgesics.—Antipyrin, acetanilid, and acetphenetidin (phenacetin) may be cautiously given when pain is not well controlled by salicylates.

They are best given in 3 to 5-gr. doses, every three or four hours, but must not be too long continued. Caffein may be combined with them to combat their depressive action. In cases of extreme restlessness or insomnia due to pain, it may be advisable to give morphin, gr. 1/8 to gr. 1/4, or codein, gr. 1/4 to gr. 1/2, hypodermically, rather than to temporize with less efficient drugs.

Vaccines and Sera

The treatment of rheumatism by antistreptococcic sera and by the subcutaneous injection of vaccines has not yielded results which warrant a recommendation of the method. The intravenous injection of non-specific bacterial or other protein, with its resulting chill, rise in fever with subsequent fall, and coincident symptoms of shock, does not appear to be justified by the average clinical results which follow the treatment.

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[1] New and Non-official Remedies, American Medical Association, 1916.

Our ideas concerning the mechanism of the development of immunity are undergoing rapid changes and it seems probable that, in addition to changes in fluids and cells which appear to be specifically related to the invading organism, other more general and less specific alterations in body fluids and ferments may take part in the struggle of the body against the disease-producing organism. Until the nature and methods of control of these non-specific processes are better understood, it seems wise to restrict the use of non-specific proteins believed to assist in their mobilization, especially in view of the fact that clinically the results obtained do not convince one as to their practical value.

Complications

Hyperpyrexia.—Sudden and alarming increase of fever, with accompanying delirium, is occasionally met with, and has been called "cerebral rheumatism." Cold baths and packs aid in allaying restlessness and in reducing the temperature.

Cardiac Lesions.—The most serious and frequent complications of rheumatism are those involving the heart, and they may occur in spite of all efforts to prevent them. The involvement of the myocardium as well as of the endocardium and pericardium has led to the use of the appropriate term "the carditis of rheumatism." The most important prophylactic against cardiac complications is absolute rest in bed and, whenever there is suspicion of cardiac involvement, the period of rest in bed should be prolonged a number of weeks after the subsidence of the acute rheumatic symptoms. Any increase of fever or increased rate or irritability of the heart occurring during the attack should direct special attention to the heart. A precordial murmur may develop coincidentally with the anemia without valvular disease, but all murmurs are to be carefully observed. Daily examination of the heart will prevent the physician from overlooking both valvular and pericardial disease, the finding of which may explain many otherwise puzzling symptoms.

The ice-bag and ice-coil applied over the precordium are extremely valuable in combating both the irritability of the heart and the pain of pericarditis. Counterirritation in the form of mustard plasters or fly blisters along the sternum have been advised. When extensive pericardial effusion occurs, the heart action may be greatly embarrassed and in extreme cases paracentesis of the pericardium may be advisable. The administration of sodium cacodylate in doses of 3 to 10 gr. daily by deep hypodermic or intramuscular injection has been followed by rapid subsidence of effusions, both pericardial and pleural, in rheumatism. The improvement has seemed to some observers so rapid as to suggest a specific action of the drug in cases of this sort; others argue that pericardial and pleural effusions frequently subside spontaneously, and that the improvement noted is not necessarily a result of drug therapy.

Symptoms of serious cardiac embarrassment call for a careful examination to determine their cause. A rapidly developing pleural effusion, which may seriously interfere with heart action, calls for paracentesis. Care must be taken to distinguish left pleural effusions from large pericardial effusions.

Cardiac insufficiency, whether muscular or valvular in origin, may require cardiac stimulants to tide the heart over the emergency. In such cases, the heart is to be treated as in incompetence arising from other causes. Digitalis is of great assistance, but should be withdrawn as soon as is consistent with safety.

Anemia.—Anemia in rheumatism is frequent and often of high grade. As soon as the acute attack subsides, iron is indicated. Iron in the form of Blaud's mass, or the citrate of iron, combined with a full diet, including vegetables and meat, is usually sufficient to insure a rapid return of the blood to normal. Arsenic, gr. 1/100, is sometimes combined with the iron, or given as Fowler's solution, — ii to x. The prolonged persistence of anemia following an attack of rheumatism suggests the persistence of the original infection, or the possibility of some lingering local infection, as in tonsils or sinuses, or occasionally the development of ulcerative endocarditis.

CHAPTER XVI

TYPHUS FEVER

ALVAH H. DOTY

Definition.—Typhus fever is an acute infectious disease, abruptly ushered in and associated with a general eruption and an early and profound involvement of the nervous system. It more markedly ends by crisis than any other disease—usually from the twelfth to the fourteenth day.

History.—There are three diseases which in the past have been responsible for great loss of life. These are plague, cholera and typhus fever.

Nothing more clearly reflects the value of modern sanitation than the control or extermination of these diseases. This relates particularly to typhus fever, which has so long been identified with overcrowding, filth and poverty that it is commonly known as "prison fever," "ship fever" and "famine fever," indicating the favorable conditions for its appearance and dissemination. Until its activity during the present European War, typhus fever had reached a remarkably quiescent state and except in Mexico it had practically disappeared from this continent.

Abundant and conclusive proof has been presented as to the connection of this disease with filth, overcrowding and an impoverished condition of the people whom it affects.

It is fair to assume that, with the knowledge we now possess concerning the source of infection in typhus fever, and the known preventive measures which may be employed, as well as the improved methods of prevention at foreign ports of departure, relating to observation, medical inspection and detention of those about to embark, this disease should in the future be far less of a menace to the public than it has been in the past, and its extermination may be hoped for.

Unfortunately a difference of opinion exists among those who have had practical experience with typhus fever concerning the degree of danger which may follow an outbreak of this disease in a populous country where modern sanitary methods are in operation. This is due largely to the fact that, while some have dealt with typhus fever both here and abroad, others have witnessed its results only in foreign sections of the world where inadequate protective measures are in force and where, chiefly from ignorance, the public extend but little or no coöperation in the prevention of disease. Often there is no evidence of official control. Under these conditions communicable diseases are quite certain to travel with great rapidity. However, this must not be accepted as an example of what will follow an outbreak of typhus fever in this or any other country where modern sanitary regulations are in force and where the public extends intelligent aid in the prevention of disease. The results which followed the outbreaks of typhus fever in New York in 1881 and 1893 bear ample evidence of this. In both instances the disease had gained considerable headway in the tenement house districts, particularly on the east side of the city, before its identity became known. Notwithstanding this, the disease was brought under control within a comparatively short time, although the equipment of the municipal department of health in the way of hospital service and other facilities was far from constituting a perfect organization, and, besides, the medium of infection in typhus fever was then unknown.

It would seem quite improbable that an outbreak of typhus fever could pass beyond control in the United States, in fact, domestic diseases constitute a far greater menace to the public here than imported ones. In view of this it would seem unnecessary to disturb the public mind in regard to the danger of this disease, at least until its arrival here; in the meantime protective measures lie in the hands of United States public officials at foreign ports of departure in the way of careful investigation before embarkation of those arriving from typhus-fever-infected sections in the interior.

Source of Infection.—It was formerly believed that typhus fever, like various other infectious diseases, was transmitted through the medium of fomites. This applies to such articles as clothing, baggage, money, and the like, which were believed to convey infectious organisms in their active state from one person to another. This theory, although erroneous, has been handed down for generations, and until recent years has been generally accepted as the common means of infection in typhus fever.

Nicolle, in France in 1909, was the first to report that typhus fever is transmitted from one person to another by the body louse (Pediculus vestimenti). His statement was subsequently confirmed by the researches of Ricketts and Wilder of the University of Chicago, and afterwards by Anderson and Goldberger of the U. S. Public Health and Marine Hospital Service, whose investigation was carried out in Mexico. This belief is in harmony with certain peculiarities of infection which are familiar to those who have dealt with typhus fever, for it is notoriously confined to persons of the class who would naturally be the hosts of these insects. For instance, during the outbreak of typhus fever in New York in 1892 and 1893, of the large number of cases dealt with by the Department of

Health, only two or three of the number were from the better walks of life. In all other cases those who contracted the disease formed part of the tenement and lodging population of the city.

Etiology.—Various protozoa and bacteria have in the past been considered as possible causes of typhus fever, but none of these has shown final tests with the probable exception of the last which was cultivated by Plotz in the laboratories at the Mt. Sinai Hospital. This organism is a non-motile, small and generally Gram-positive pleomorphic bacillus. Its length is from 0.9 to 1.9 microns and its average breadth two-fifths as great. It is not acid-fast, does not produce spores and produces no visible capsules. It does not pass through the Berkefeld filter.[1]

The bacilli are strictly anaërobic and are first cultured by adding the blood of the patient to melted glucose serum agar, contained in long test tubes. The colonies are usually numerous in cultures made from blood taken during the first days of the disease, and generally negative from blood taken at the crisis and uniformly negative from blood obtained from more than thirty-six hours after the crisis.

The blood taken early in severe cases may yield several hundred colonies from each cubic centimeter, but as a rule only a very few develop, and in about 50 per cent of mild endemic cases no culture develops. Only a highly trained bacteriologist with exact knowledge of the technic can hope to obtain a culture. Up to the present time no others except those trained by the Mt. Sinai workers have been successful.

Successful results have also been obtained from the blood of infected guinea pigs and monkeys.

Olitsky has made extensive studies on the immune bodies in convalescent cases and found that complement fixing antibodies and agglutinins developed rarely before the crisis, but most extensively between the third and tenth day after. The antibodies, after reaching the maximum, were found to diminish gradually.

Persons who have been in close contact, but who have not had any symptoms, sometimes develop antibodies. Those who have not had this disease so far as they know and have not knowingly been in contact with cases have antibodies very rarely.

The cultures in the glucose serum media lose their virulence almost immediately, and these cultures do not have the property of immunizing susceptible guinea pigs and monkeys. This is peculiar, as the animals have immunity when they have recovered from the disease. The use of the vaccine must, therefore, be understood as still in the experimental stage, and there is no proof yet of its being of value. The reports of its use in Mexico thus far are not encouraging. The European results appear to be favorable but have not been fully reported. Our present information points very strongly to the bacillus isolated by Plotz being the causative microörganism, but until cultures are obtained which keep their virulence or have the power to immunize human beings or suitable animals a doubt will remain. It is hoped that the investigations which are being carried on in Europe will determine conclusively the nature of this bacillus.

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[1] Wolbach and his coworkers were entirely unable to substantiate the work of Plotz. Wolbach believes typhus to be due to an organism of the Rickettsia type.—Editor.

Incubation and Invasion.—The incubation of typhus fever usually covers a period of from eight to twelve days.

The invasion is abrupt and very brief, and in this respect is particularly characteristic of this disease. A person may retire apparently in good health and be seized during the night or in the morning with a headache and a chill or a chilly sensation. Headache is practically always present. The face becomes flushed and the conjunctivæ are congested. These are early and constant signs of typhus fever. To this may be added an early involvement of the mental faculties. It is the latter which has given the name of typhus to this disease, the word typhus indicating stupor and relating to the confused condition of the mind.

Temperature.—The temperature curve is very characteristic, and is best understood by a study of the accompanying charts, which are typical and indicate the range of temperature in actual cases which occurred during the epidemic of typhus fever in New York City in 1892-1893.

The temperature rises rapidly and usually attains its height at 104° or more, about the fourth or fifth day of the disease, when it becomes stationary, with some diminution in the morning. After the ninth or tenth day, in favorable cases, the temperature begins to decline, and usually continues so until recovery. From the twelfth to the fourteenth day the temperature as a rule abruptly drops to normal or subnormal; this is particularly characteristic of the disease, for typhus usually terminates by crisis at this time.

The Eruption.—On the second to the fourth day of typhus fever the characteristic eruption appears; the diagnosis of no other disease depends more fully upon this sign. Without it a diagnosis cannot consistently be made.

While there are other forms of infection which may produce an eruption somewhat similar to typhus fever, that of the latter disease may as a rule be confirmed if sufficient time is given for this purpose. The eruption of typhus fever is quite apt to be present when the physician first sees the patient.

The true or diagnostic eruption of typhus fever is petechial, due to a minute hemorrhage in the center of the spot. It can be easily understood that such a condition would occur in the presence of great prostration and weakness of the vascular system. The eruption is general over the body, and may be particularly well studied on the flexor surface of the forearm or about the shoulders. The eruption does not occur in successive crops as in typhoid fever, but as one crop, although it may be irregular in arriving at its completion. It may last eight or ten days, and is usually present when death occurs, prior to the end of the second week. In some cases a slight desquamation may follow. However, this is of no diagnostic importance.

A more minute description of the eruption is as follows: At first it does not assume its true character, but appears as a rash which sometimes may be mistaken for measles. The spots are irregular and vary in size from a pea to those which are much smaller. They may be isolated or rather grouped in patches, and do not at first present the characteristic dark rose-colored appearance, and may even disappear on pressure. The eruption generally presents itself first on the chest and abdomen, and afterwards on the arms and thighs. On the face and neck it is not only pronounced but frequently may not be detected. This has been ascribed to the very vascular condition of this part of the body, added to the extreme hyperemia which occurs in typhus fever. There is some reason to believe that this is the proper explanation. In addition to the eruption above referred to, a mottling of the skin may occur.

The early eruption soon undergoes a change. The spots become darker in color, and do not disappear on pressure. Subsequently there appear in the centers of the spots dark bluish points known as petechiæ, due to minute extravasations of blood. This practically represents the true eruption of typhus. To complete the picture, a dusky or congested appearance of the surface of the body is present, whereas in typhoid fever, for instance, the skin retains its normal color, or is even paler.

Prognosis.—Age has largely to do with the prognosis. Very young children do not often die from it, and those who succumb are usually beyond early youth; after this the mortality increases, and at the age of fifty the mortality is generally from 40 to 50 per cent, particularly among those who are addicted to the excessive use of alcohol or have organic diseases or other debilitating causes. One attack of typhus fever generally confers immunity.

There is one factor present in typhus fever which is probably more constant than in any other disease, that is the termination by crisis about the fourteenth day. It is very important that this should be borne in mind, particularly in doubtful cases; furthermore, the prognosis of typhus fever should be very guardedly given, for some of the most serious and apparently most hopeless cases at the end of the second week may fall into a deep and refreshing sleep, after which there is a rapid change for the better. On the other hand, many patients who have safely passed the crisis subsequently succumb, although they may appear to be on the road to recovery.

Preventive Measures.—If the body louse is the sole medium of infection, its destruction is the most effective means of preventing the extension of typhus fever. Shipley of Cambridge, England, finds that body lice cling tenaciously to the clothing, and, while they may not be found on the surface of the body, the inner side of the wearing apparel next to the skin may be covered with them.

Various means have been suggested for the destruction of the body louse and various applications are advocated, a large number of which cannot be depended upon. It should be borne in mind that not only the lice but the nits must be destroyed to ensure safety, and this requires very active measures. If the clothing is worthless it is far better that it should be destroyed by incineration; otherwise steam or boiling water may be used. The latter agents may be depended upon for the destruction of this insect and nits, provided there is a proper exposure.

Treatment.—There appears to be no specific for typhus fever, and there is but little that can be done in the way of medication except by the use of remedies to relieve the insomnia or delirium, to reduce the fever and strengthen the heart. Medicine should be administered with great caution, for there is but little doubt that in many instances the chance of recovery which the patient may have had has been overcome by the injudicious use of drugs. Certain preparations have been suggested by various writers as particularly valuable in the treatment of typhus fever. The author's experience does not confirm this.

Cold applied to the head is usually grateful, and cold sponging or cold baths are frequently employed with good effects, although the latter procedure by disturbing or exhausting the patient is often contra-indicated. The result in such cases should determine if this treatment is to be continued.

There is no simple measure more valuable to the patient than fresh air, and there is no reason why those sick with this disease should not, under proper bodily protection, be removed outside on to verandahs or placed in tents.

During the outbreak of typhus fever in New York City in 1892-1893 the hospital accommodations for this disease were inadequate and a tent service was provided in the grounds of Bellevue Hospital during the winter months. The difference in the mortality of cases treated in the hospital and in the tents soon became noticeable, being far less among those treated in tents. It must be borne in mind that in this disease we deal with a profound systemic infection, and there is abundant and continued proof that fresh air and its stimulating and tonic effects are of inestimable value in these conditions.

What has just been said concerning the treatment of typhus fever is apparently in accord with the views of Dr. George G. Shattuck, of Boston, whose wide experience and valuable service during the outbreak of this disease in Servia is well known. The following are extracts from a statement made by Dr. Shattuck:

"It seems to me that the Servian epidemic confirmed the view that unhygienic surroundings and insufficient food by lowering the vitality tend to cause a high mortality."

Dr. Shattuck also believes that death occurring late in the disease is due to exhaustion associated with a gradually failing circulation and an inability to assimilate food. Dr. Shattuck is quite satisfied that medicine cannot be depended upon except in special instances, such as heart failure, restlessness, etc., and then it should be used with great care. He refers particularly to the importance of careful nursing and the probable value of intravenous injection of 8 to 10 ounces of a salt solution—particularly in patients who present a dried-up appearance, suggesting a lack of water in the tissues.

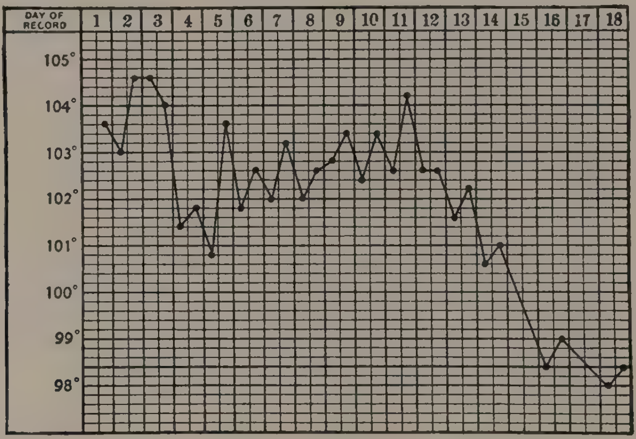

Fig. 1.—Case of Typhus with Gradual Decline of Temperature, followed by Recovery.

It would seem, therefore, that the treatment in typhus fever relates chiefly to supporting measures, proper nourishment, careful nursing, and hygienic surroundings.

Differential Diagnosis.—Typhus fever may be mistaken for typhoid fever, measles, cerebrospinal meningitis; less frequently pneumonia, malaria, and in some instances other acute infectious diseases.

In typhus fever the invasion is abrupt, in typhoid fever it is prolonged. This is a very valuable point to bear in mind in deciding between these two diseases which most frequently call for a differential diagnosis.

In typhus fever the disease begins with a rapid rise of temperature, chill or chilly sensation, profuse headache, and early and great prostration and involvement of the mental faculties, a suffused congestion of conjunctivæ and an eruption which appears on the second or third day of the disease.

In typhoid fever the temperature rises slowly and no pronounced impairment of the mental faculties usually occurs in the early stage of the disease, no injection of conjunctivæ takes place and the eruption does not appear until the second week of the disease. Besides, in typhoid fever there are symptoms referable to the abdomen and the Widal test is available.

In typhus fever the true eruption is petechial, and generally distributed about the body, appears in one crop only, and does not disappear on pressure, whereas the eruption in typhoid fever is generally confined to the abdomen, is rose-colored and papular, occurs in successive crops, and *does* disappear on pressure.

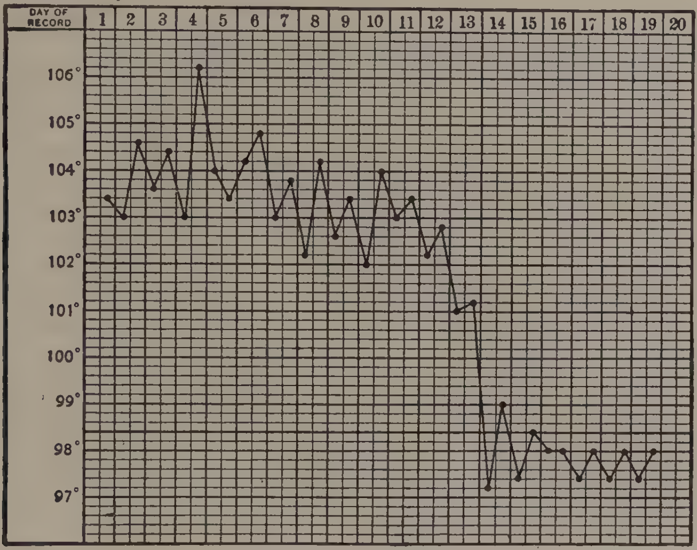

FIG. 2.—CASE OF TYPHUS WITH DECLINE OF TEMPERATURE BY CRISIS, FOLLOWED BY RECOVERY.

The differential diagnosis between typhus fever and measles should be easily determined, particularly after a day or two. Typhus usually affects the adult, while measles generally occurs during childhood. While measles appearing in the adult may call for more caution in the differential diagnosis, the profuse eruption, the conjunctivitis with pronounced catarrhal symptoms and little or no involvement of the mental faculties enerally indicates the diagnosis.

If care is employed, malarial fever can hardly be confounded with typhus fever, at least no longer than is necessary to observe the periodicity and to detect the plasmodium.

Meningitis, particularly in the cerebrospinal form, may for a short period in some instances be mistaken for typhus fever. However, the invasion of cerebrospinal meningitis is more abrupt than typhus fever; it usually occurs with really no premonitory symptoms; vomiting, which is a very common symptom in cerebrospinal meningitis, does not, as a rule, occur in typhus. Rigidity of the nape of the neck and opisthotonos constitute the most important signs in cerebrospinal meningitis, whereas they have no special relation to typhus fever. Furthermore, in cerebrospinal meningitis death usually takes place in from one to three days, and in typhus fever the duration of the disease is much longer. An eruption does not always occur in cerebrospinal meningitis. When present it has no definite or special form and can be easily diagnosed from that of typhus fever.

A careful examination of the chest will usually identify pneumonia, which is not a complication of typhus fever, the pulmonary involvement in the latter disease being usually confined to bronchitis.

In one fatal case under the author's observation, where the patient had an eruption which was extremely suggestive of typhus fever, the skin having in addition to the eruption a cyanosed appearance, the autopsy showed a very extended suppuration of the right kidney, from which was removed a concretion half the size of a hen's egg. While cases of this kind are rare, they should be thought of when the presence of typhus fever is suspected, particularly if there is no history of exposure to this disease and no outbreak has been reported.

Brill's Disease.—In 1910, Dr. Nathan E. Brill, of New York City, who had previously (1896) referred to this subject, reported in the *American Journal of the Medical Sciences* a study of 221 cases of "an infectious disease of unknown origin and unknown pathology characterized by a short period of incubation (four to five days), a period of continuous fever, accompanied by intense headache, apathy and prostration, a profuse and extensive erythematous, maculopapular eruption, all of about two weeks duration—whereupon the fever abruptly ceases either by crisis within a few hours or by lysis within three days, when all symptoms disappear."

During the following year (1911) Dr. Brill reported in the same journal further observation concerning this disease.

Dr. Brill's reports attracted the special attention of Dr. Anderson and Dr. Goldberger. In reference to this Dr. Anderson states as follows:

"We were struck by the very remarkable resemblance between the disease of Brill and typhus fever as observed by us in Mexico and as observed by one of us in certain places abroad. For this reason we endeavored to gain access to a case of Brill's disease in order that we might determine if possible its relationship to typhus. A case was finally seen in the ward at Mt. Sinai Hospital and blood was drawn from the arm vein of this patient and used for the inoculation of monkeys. One of these animals after an incubation period of ten days developed a fever which reached its maximum six days later and fell by a rapid crisis fourteen days after the rise began."

Dr. Anderson concludes that typhus fever and Brill's disease are identical. He also reports that Roger Lee, in a study of cases recorded in the Massachusetts General Hospital conforming to Brill's disease, covering a period from 1902 to 1912, believes that typhus fever in a mild form has prevailed in Boston and vicinity during that time. He states that, in his study of the records of 1,404 cases of continued fever in that institution of greater duration than seven days, 28 cases corresponded extremely closely with Brill's description of typhus fever; this gives a ratio of 1 case of typhus to 47 cases of typhoid fever.

As a result of the several investigations referred to, particularly on the part of Anderson and Goldberger, it is now generally accepted that typhus fever and Brill's disease are but different types of the same affection.

While it is true that the bacteriological investigation of Anderson and Goldberger seems to justify this belief, and although the clinical pictures of typhus fever and Brill's disease are more or less similar, and there may be no other explanation for the presence of the latter disease, there are certain points in connection with the subject which should receive careful consideration before a final conclusion is made concerning the exact relation between these maladies. It may be noted that there are some important points in connection with Brill's disease and typhus fever which are unlike. For instance, in typhus fever there is almost always an early and profound impairment of the mental faculties, whereas in Brill's disease this either does not occur or is present only in exceptional cases; furthermore, typhus fever is a dangerous and actively communicable disease involving a high mortality, whereas in Brill's disease patients rarely die and there is practically no evidence that it is communicated to others.

During the past thirty-five years there have been two epidemics of typhus fever in New York City, one during the year 1882 and the other in 1892-1893. In both epidemics the origin of the outbreak was clearly and definitely traced to immigrants recently arriving on incoming foreign vessels; there is also definite proof that after these outbreaks subsided there were no further reported cases of typhus fever in New York City.

In Dr. Brill's report in the *American Journal of the Medical Sciences* in 1910 he states:

"Clinically this disease resembles typhus fever more than it does any other disease, and I should have thought that I had offered nothing to our nosology if it had been proven that typhus fever had lost its virulence, that it was constantly present in the community, that it was not communicable, that when it was present epidemics did not occur, and that it was no longer a grave fatal disease, but that typhus fever as great Masters of Medicine have taught us, and as I have seen it, was such a conception would be unjustifiable, therefore I believe this disease is not typhus fever."

Dr. Brill and many others believe that this unknown disease has been more or less continually present in New York City as well as in other sections of the United States for many years, yet there is no recorded instance where it has taken on the form which is typical of what we know as typhus fever. Neither has it caused an outbreak of this disease and practically is associated with no mortality. In other words, Brill's disease is shown to be a benign affection and apparently not communicable.

The statement that Brill's disease and typhus fever are identical is more or less misleading and disturbing, for it indicates that a dangerous communicable disease is commonly present. On the other hand this may lead to the belief that typhus fever is not a serious menace to the public health and is likely to encourage carelessness upon the appearance of what may be called true typhus fever.

If Brill's disease does not take on the character or danger of typhus fever and so far as the public health is concerned is practically harmless, why is it not sufficient to let it be known as Brill's disease?

CHAPTER XVII

INFECTIOUS CATARRHAL JAUNDICE

George Blumer

Epidemiology and Etiology.—Local outbreaks of jaundice have been described in the United States since 1812, but the literature on the subject gives no adequate idea of the frequency of the condition. The writer has collected information covering over 100 outbreaks, mostly along the Atlantic seaboard and in the Middle West, but by no means confined to these regions. Judging from published reports, the disease also occurs in European countries.

The exact nature of the disease has not been determined, though many writers have assumed that it is identical with Weil's disease or spirochetosis icterohæmorrhagica. While there are a few reported outbreaks which may be true spirochetosis, there is no proof that this is the case in the majority so far reported; on the contrary, attempts to isolate spirochetes from the blood or urine of patients have been uniformly negative in the hands of competent bacteriologists. The fact that rats in infected territory may harbor the Spirochæta icterohæmorrhagiæ, while interesting and suggestive, cannot be regarded as proof. Furthermore, the clinical course of the disease in most of the reported outbreaks is different from that of Weil's disease.

The disease occurs, as a rule, in rather sharply localized endemic foci and epidemiologically is more like poliomyelitis than the exanthematous infections. As a rule it is a seasonal disease occurring in the fall and early winter, but it may occur at any time of year. Many reports cover outbreaks affecting only half a dozen patients, while in others from 30 to 300 or 400 cases occurred in an infected district. In only two states, New York (1922) and Maine (1888) do there seem to have been extensive outbreaks covering many scattered foci in a single season. The disease appears both in cities and in remote country districts. In the latter there is some evidence which suggests the incrimination of the little red schoolhouse or its modern prototype as a center of dissemination.

No age or sex is exempt but in many outbreaks the great majority of the patients have been young children.

Symptomatology.—The symptomatology is not unlike that of an exaggerated catarrhal jaundice. The onset may be either gradual or sudden and the early stages are often associated with severe headache and distressing pains in the back and limbs. Gastro-intestinal symptoms usually appear early. There may be abdominal pain and there is usually complete anorexia with nausea and vomiting which may persist for several days. The bowels are usually constipated and the stools may contain some bile or may be totally acholic and clay-colored. Fever is very variable. In some outbreaks, it has been absent in the majority of patients; in others, it has been present from the onset but moderate in degree. In still others, high fever has been common. The duration of the fever is, as a rule, about five days but it may last for ten days or even longer. The jaundice does not appear until the disease has lasted for several days, four or five usually, is not very intense and may be associated with a slow pulse, somnolence and itching of the skin. It may persist for weeks. It may be absent in a certain proportion of the patients. General and circulatory asthenia may be prominent. Recovery may be rather slow; in some outbreaks four or five weeks elapse from onset to complete convalescence; in others, patients recover in less than three weeks. The mortality in most outbreaks is nil. When fatalities have occurred they have generally involved feeble infants or pregnant women. At times patients have developed a state of cholemia which clinically resembled acute yellow atrophy.

The physical signs, aside from jaundice, have been those associated with a general infection and, in many outbreaks, a slightly enlarged, tender liver and an enlarged spleen. There are no sequelæ as a rule, though late nephritic complications occur occasionally. Relapses seldom occur. Hemorrhagic manifestations are so rare in most of the reported cases that one suspects that the occasional outbreaks in which they were common may have been true spirochetosis. One outbreak reported in one of the Southern States as infectious jaundice was probably blackwater fever.

Prophylaxis.—So long as the causative agent of the disease is unknown, prophylaxis must be based on general principles. The disease should be reportable and now is in a few states. When it occurs in a community, patients suffering from it should be isolated as there is pretty clear evidence of contact infection. In many outbreaks catarrh of the upper air passages is present, suggesting that these may be the portal of entry. Care should therefore be taken to avoid contamination from this source and all secretions from the nose and throat should be received on paper napkins or old rags which may be burned. Nurses should practice the technic of an isolation ward. The excreta should be sterilized until further knowledge shows whether this is necessary or not. The dishes used by the patient should be kept separate and should be thoroughly scalded. Bedding, night clothes, towels, etc., should be sterilized by heat or by the usual chemicals employed for this purpose.

Treatment.—The treatment is purely symptomatic and is essentially that of an infectious fever.

For the severe headache the ice-cap is of service. In patients with marked back and limb pains it may be necessary to employ anodynes, preferably the coal-tar preparations, though these must be used with caution in patients with circulatory weakness. Rarely codein, paregoric or even morphin will be required. The gastro-intestinal symptoms are best controlled by a soft, easily digestible diet which should be poor in fat. Preliminary purgation is perhaps desirable, but the continued use of purgatives is apt to increase the abdominal pain and irritation (Waters). Vomiting may be controlled by chloroform water (Waters), bismuth or lime water. Where vomiting does not preclude it, water should be freely administered. Cardiac stimulation may be required in some patients.

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CHAPTER XVIII

ROCKY MOUNTAIN SPOTTED FEVER

JOHN F. ANDERSON

Rocky Mountain spotted fever is an acute infectious disease characterized clinically by headache, pains in the back, joints and extremities; fever of a remittent type; an eruption, at first macular, later becoming petechial, and with a tendency to gangrene of certain parts of the skin. The disease is transmitted by the bite of an infected tick.

The disease occurs in the Rocky Mountain and Pacific states, east of the Coast Range Mountains. The great majority of cases occur during the tick season, from early spring to midsummer. The first cases are usually noted after the snow melts, and increase in number as spring advances. The virulence of the disease shows marked variations for different sections, as is shown by the high case mortality in the Bitter Root Valley of Montana, and the comparatively low mortality in the region of the Snake River in Idaho.

The researches of Ricketts, King, McClintic and of Fricks have conclusively demonstrated that Rocky Mountain spotted fever is transmitted by the bite of the wood tick, *Dermacentor Andersoni*. The work of these investigators has shown the presence of infected ticks caught at large and that the reservoir of infection is probably in the small wild animals of the infected regions.

While we know that the tick transmits the disease we, as yet, do not know the specific etiological agent, so that the statement of Ricketts still holds that the disease is "a generalized invasion of the body by a microorganism which, as yet, is unrecognized and uncultivated."

The disease bears a close clinical resemblance to typhus fever, and cases of the two diseases occurring in the same locality would be, at the bedside, difficult to differentiate. Fortunately the inoculation of the guinea pig with blood from a spotted fever case induces in that animal, with great regularity, a characteristic reaction so that the diagnosis can be satisfactorily determined.

While Rocky Mountain spotted fever has been observed for a great many years and a great many suggestions have been offered for the treatment of the disease, we are, as yet, without knowledge of any specific treatment. But the fact that the researches of the last ten years have shown the manner in which the disease is conveyed has enabled us to formulate measures which offer distinct promise of the eventual control and perhaps eradication of the disease.

The treatment of the disease is best discussed by first taking up the measures for the prevention of the disease, and then those for the treatment of the individual after the onset of illness.

Prophylaxis.—By reason of the fact that the disease is conveyed by the bite of an infected tick, all our measures for the prevention of the disease are focused upon ways to prevent persons being bitten by those insects and upon the eradication of ticks in endemic foci of the disease.

Before we take up the general or community measures which have for their object the eradication of the ticks, we shall consider those prophylactic measures which apply to the individual. The first of these is avoidance of localities, so far as possible, within the endemic foci of the disease during the tick season.

For those who must enter the infected region certain precautions are suggested. They should avoid as much as possible personal contact with brush, weeds, grass and animals which now harbor ticks. Tickproof clothing should be worn and the clothing and body should be examined as often as possible to see that no ticks are thereon. If a tick is found attached to the body it should be at once removed and the site should be cauterized immediately with 95 per cent carbolic acid or with a stick of silver nitrate. Care should be taken in removing the tick not to leave the head embedded in the skin. The tick may usually be readily removed by applying ammonia water, turpentine, liquid petrolatum, or kerosene, and it should be at once destroyed as it has been demonstrated that the bite of a single tick may transmit the disease.

The really brilliant work of the Bureau of Animal Industry in limiting and decreasing the spread of Texas fever of cattle, which disease is also conveyed by ticks, has shown what may be hoped for in our efforts to control Rocky Mountain spotted fever. These efforts all have for their object the decrease in the tick population. As the stock furnishes a food supply for the tick during the various phases of its life history, and as the female tick is fertilized during feeding, the killing of ticks on cattle, horses, and other stock, by "dipping" in some approved "dip," is of great importance. The dipping of all stock in the region of the disease should be required by law from early spring to midsummer. The clearing of the land of brush and then burning will destroy large numbers of ticks and their eggs.

Fricks in 1913 showed that even when ticks are placed in the wool of sheep they soon die, and in later papers he has brought out convincing data as to the importance of sheep grazing over infected land for the destruction of ticks. He considers that the grazing of sheep results in the removal of undergrowth and the destruction of "good tick country" by close grazing, in the removal or disappearance of other large mammals, both domestic and wild, from the sheep range; and in the destruction of ticks by the grazing sheep; and finally, it places the problem of tick eradication on an economic basis.

As investigations have shown that the small animals of the infected region may harbor large numbers of ticks, and may also be susceptible to the disease and thus maintain a reservoir of infection for ticks, it becomes of great importance that the number of small animals be reduced as much as possible. For this reason bounties should be offered for the killing of the small animals, particularly the ground squirrel, chipmunk, and others.

Treatment.—There are few diseases for which more drugs have been recommended than for spotted fever and as yet we are without a satisfactory specific treatment, although attempts have been made to produce a serum for this purpose. Ricketts used a serum prepared from the horse by immunizing with blood from infected guinea pigs; the serum was found to have some protective properties and also apparently exerted some influence on the developed disease in guinea pigs, when given early and in large doses. Results of its use in human cases did not offer much promise of its value.

From the time of the bite by an infected tick to the development of definite symptoms, there is an incubation period of from three to nine days, during which time, or most of the time, the patient may feel entirely well, or he may experience obscure and indefinite sensations, especially constipation and more or less headache and general malaise. At this time the patient may not know that he has been bitten by a tick, the tick or tick bite (if the tick has fed and dropped off) often not being discovered until the characteristic symptoms develop. Usually, when the physician first sees these cases, the patient is complaining of considerable headache and pains in the legs, back, etc., and has from one to three degrees of fever. In the Montana cases, however, the pains are not a very prominent early symptom (Dodds).

When first seen the patient should be given a hot bath and ordered to bed. A generous dose of *calomel* and *soda,* to be followed by an efficient *saline,* should be given at once, and the patient instructed to *drink freely of water.*

A great number and variety of drugs have been suggested for the relief of the *pains* which are a more or less constant accompaniment of this disease, especially during the first ten days. Probably the best remedy for the relief of the pains is *aspirin* (McCalla, Mills, Numbers, Smith, Springer, Stewart), in doses of 0.32 to 0.65 gm. (5 to 10 grs.), repeated every two to four hours. The size and frequency of dose should depend entirely on the effect it has on the pains, care being exercised to avoid overdosage and to follow each dose with a copious draft of water. Phenacetin (Bowers, Dodds, McCalla, Numbers, Shirley, Smith, Taylor), salol (Shirley), and the salicylates (Bowers, Mather, Mills, Numbers) may also be used, while some physicians resort to the use of acetanilid (Taylor), the bromids (Numbers, Springer), quinin (McCalla, Mooser, Taylor), and antipyrin (Springer), in varying dosage and combinations. In the more malignant type of the disease some use dry heat, or sponge the patient with a hot 2 to 5 per cent solution of phenol (McCullough), and more frequently resort is made to the use of morphin (Dodds, Kellogg).

In the writer's opinion, however, it is rarely necessary or advisable to prescribe morphin or other form of opiate in these cases. If the bowels have been properly cleansed, there are few cases that will not be made comfortable by the intelligent use of aspirin and hot baths (Bowers, Mills), or dry heat.

If the remedies given to relieve the pains are not also sufficient to keep the *fever* within reasonable bounds, *hydrotherapy* (Bowers, Dodds, McCalla, Mills, Numbers, Pease, Smith, Springer, Stewart) may be resorted to with confidence. Cold sponge baths and cold packs are sufficient in most cases of hyperpyrexia; tubbing can be used where these fail to reduce the temperature. Mills recommends bathing the patient in hot water, gradually bringing the temperature of the water up to 120° F.

In severe cases the eruption is often marked in the throat and on the palate, and the mouth, tongue, and throat are dry, foul, and distressingly uncomfortable. In such cases a mild antiseptic mouth wash, containing also glycerin and perhaps lemon juice, if used frequently as a gargle or swabbed over the parts, will contribute materially to the patient's comfort.

As *constipation* is practically always present during the entire course of the disease, a gentle laxative should be exhibited daily. Nothing serves better for this purpose than the *sulphate of magnesia* (Smith, Springer, Stewart), in sufficient doses to produce one or two daily stools.

Regardless of the fever, the nurse should be instructed to give the patient frequent sponge baths, followed by alcohol rubs, to maintain an active and comfortable condition of the skin, and the position of the patient should be changed frequently to prevent hypostatic congestion and slough formation. If the skin itches or burns, sponging with a strong soda solution, or applying an ointment of oil of eucalyptus, 1 part in 8 parts of vaselin (Springer), will be cooling to the skin and relieve the itching.

The *heart* often shows signs of weakness and dilatation, particularly in the older patients, and this condition calls for the exhibition of *digitalis* and *strychnin,* preferably given hypodermically. Taylor advises the routine use of strychnin as soon as the pulse rate begins to rise, to be continued through convalescence to support the weakened heart muscle.

Bronchitis complicates many of the cases, and in alcoholics pneumonia is liable to occur. Edema of the lungs is also reported as a fatal complication. Cases having lung complications require special care in nursing, frequent change of position in bed, and otherwise attending to the comfort of the patient and to the hygiene of his environment. The heart usually goes bad in these cases and needs constant watching. Whisky, egg-nog, etc., may have to be given in addition to digitalis and strychnin to stimulate and support the heart, and oxygen may be of benefit in combating the carbonic acid poisoning.

Nephritis is not a common complication, but nearly all of the severe or fatal cases develop uremia, or at least a profound toxemia. Hence the advisability of encouraging all patients to drink freely of water, and also the daily exhibition of moderate doses of magnesium sulphate or other laxative. In the severe cases, if the patient's condition will permit of it, the hot bath or hot pack will be of benefit by promoting activity of the skin and relieving the overtaxed kidneys. The slow saline enemata, drop method (Pease), or normal salt solution given subcutaneously, may be of special service.

In the Montana cases cerebrospinal symptoms are frequently encountered (Kellogg), and delirium is practically always present in the severe cases. One case is reported where the patient developed an acute mania which lasted about two months after convalescence. Hydrotherapy, sedatives, and restraining measures limit the physician's usefulness in these cases.

When the eruption involves the palate and pharyngeal walls, as it sometimes does in the Idaho cases, gangrene is apt to develop and prove a serious complication, practically always fatal. In addition to the cleansing and antiseptic mouth wash suggested above, removal of the necrotic tissue may make the mouth less foul, and thus add to the patient's comfort. Gangrene of the scrotum and lobule of the ear may develop in the very severe cases, the treatment being surgical.

The early and continuous use of quinin in large doses is recommended by Anderson, Mooser, and Taylor, with the claim that it has a favorable influence on the course and severity of the disease, but this claim is not sustained by the experience of many other physicians.

In using the quinin treatment it is recommended that the sulphate be given in 1.0 to 1.32-gm. (15 to 20-gr.) doses, repeated every four to six hours. If the sulphate disturbs the stomach, the bimuriate may be given hypodermically, 1.0 gm. (15 gr.) every six hours (Anderson), or the quinin may be combined with sodium benzoate, 1.0 to 1.32 gm. (15 to 20 gr.) of the former to 2.0 to 2.65 gm. (30 to 40 gr.) of the latter per day (Taylor). Mooser gives 2.0 gm. (30 gr.) twice daily for about one week, then gradually reduces the dose until temperature remains normal. Kellogg and Reed have each used sodium cacodylate with apparent success in a single case.

The *diet* requires careful supervision from the beginning of the disease to prevent intestinal fermentation, and later properly to sustain and nourish the patient. If the bowels are kept open a fairly generous *soft diet* may be allowed most patients throughout the entire course of the disease. Milk, buttermilk, sauer milch, or Bulgarian buttermilk, koumiss, broths, soft eggs, soft toast, etc., are usually well borne and relished by the patient, and can be repeated every two to four or six hours.

SUMMARY

To summarize, the chief features in the treatment of spotted fever are as follows:

1. Preventive measures, by avoiding exposure to infection, and the various methods for destroying ticks.
2. Initial dose of calomel and soda, followed by a saline.
3. Aspirin for pains.
4. Hydrotherapy for fever.
5. Sulphate of magnesia daily, and drink freely of water.
6. Strychnin, digitalis, and whisky for weak heart.
7. Soft diet.
8. Bitter tonics, hydrochloric acid, and iron in convalescence.

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CHAPTER XIX

INFECTIOUS MONONUCLEOSIS

THOMAS P. SPRUNT

The disease variously designated as "infectious mononucleosis," "acute benign lymphoblastosis," or "glandular fever" is characterized by a sudden or a gradual onset with malaise, vague aches and pains, moderate fever, a general enlargement of the lymph-nodes and of the spleen, and an unusual blood picture. The leukocyte count, which may be normal early in the disease, gradually increases and reaches its maximum with the highest point of the temperature. This leukocytosis is due to an increase in the mononuclear elements of the blood, almost all of which are apparently of lymphoid origin and which differ from the normal small lymphocytes in the larger amount and slightly changed staining reactions of their protoplasm and perhaps also in the shape of the nucleus. The total count may vary from 12,000 to 30,000 cells with from 60 to 80 per cent of mononuclears.

The clinical picture is usually that of a mild or moderately severe febrile illness with no especially striking features until the blood examinations are made. Then, if one is not familiar with this syndrome, grave fears may be entertained that the patient may be in the early stage of an acute lymphatic leukemia. The patient, however, is not as ill as one would expect in leukemia, there is no hemorrhagic tendency, there is no anemia and the blood smear differs from that of leukemia in an absence of numerous smudges of fragile cells and in the variation in the slightly pathological lymphocytes, whereas in leukemia the cells usually bear a close resemblance to each other. The criterion of greatest value is the course of the disease, which in infectious mononucleosis is benign and in leukemia progressive to a fatal termination.

The duration of the fever in infectious mononucleosis is from one to several weeks. With the disappearance of fever the patient feels comfortable, his strength returns gradually, the lymph-nodes and spleen slowly become smaller and the blood picture comes back to normal, but, as a rule, only after several months.

The etiological agent is unknown. The Wassermann reaction is negative. Cultures from the blood and from excised lymph-nodes remain sterile. Animal inoculations have been negative. There is frequently a slight pharyngitis or tonsillitis or rhinitis and cultures from the nose and throat have shown the varied flora that one might expect. From the frequency of such lesions and of early enlargement of the cervical nodes it has been suggested that the portal of entry is through the mucous membrane of the upper respiratory tract.

Its nosological classification is at present uncertain. Is it a definite entity? Is it a specific infectious disease as it appears to be? Is it a type of reaction to any one of a number of infecting agents? May it be an unusual reaction on the part of the patient to an ordinary organism which in the average person calls forth the usual type of blood and tissue response? Is there any relationship to leukemia? These questions cannot receive categorical answers now. There is one bit of data which indicates that it is not an unusual response to an ordinary infection. In one of our cases during convalescence when the polymorphonuclear leukocytes and lymphocytes were almost equal in numbers, the patient became acutely sick with follicular tonsillitis and promptly showed a definite polymorphonuclear leukocytosis.

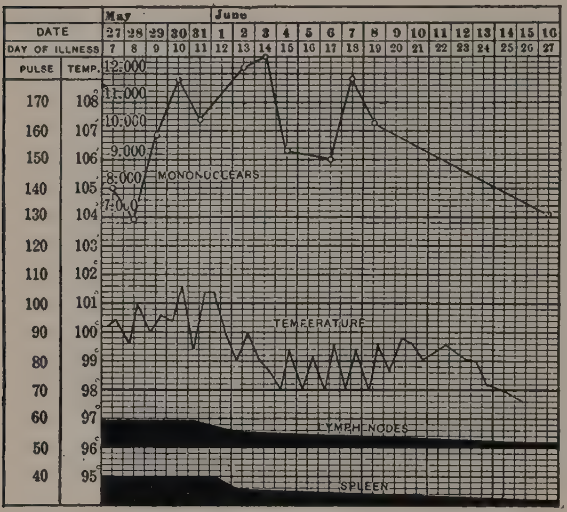

FIG. 1.—CHART SHOWING TEMPERATURE CURVE, CHANGES IN ABSOLUTE NUMBER OF MONONUCLEAR CELLS AND VARIATIONS IN SIZE OF LYMPH-NODES AND SPLEEN DURING DISEASE. (Reproduced through courtesy of Dr. Longcope and of Lea & Febiger.)

The literature is somewhat confusing by reason of the fact that series of these cases have been published under various designations. Bloedorn and Houghton speak of it as acute benign lymphoblastosis. Tidy and Morley in England and Morse in this country report cases under the title of glandular fever and consider them identical with the cases described by Pfeiffer, Park West and others. We are inclined to agree with Longcope, the most recent writer on the subject, that such an identity is not now certain. Glandular fever is described chiefly in children and as occurring in epidemics. Most of the reported cases of infectious mononucleosis have been in adults and of sporadic occurrence. In comparing descriptions of the cases, the lymph-nodes in infectious mononucleosis are not swollen to the large proportions frequently found in glandular fever. Further blood studies are desirable in epidemics of the latter disease.

Treatment.—The evidence at present indicates that infectious mononucleosis is a self-limited disease, running a usual course and that attempts at specific therapy do not materially modify its progress. Osler reported a satisfactory recovery after four intravenous injections of arsphenamin. Several cases have been treated with sodium cacodylate. Longcope mentioned one case in which the Roentgen rays were used. Most of the cases have recovered promptly with symptomatic treatment alone.

During the febrile period, the patient should be kept at rest in bed, with a bland diet and with abundant fluids to drink. A sufficient laxative may well be given at the beginning and satisfactory bowel elimination maintained throughout. For the headache, aching pains or other discomfort, aspirin or other mild analgesics may be used, or, if necessary, codein in ¼ or ½ gr. doses.

Symptoms arising from the nose and throat may require special treatment. In the milder cases a gargle or spray of salt, soda and borax, ʒss of each in a pint of warm water, helps to keep the mucosa clean and a 10 per cent solution of protargol may be applied once or twice a day. In severe cases with much exudate and false membranes, potassium permanganate (1:8,000) and hydrogen peroxid, one quarter or half strength may be used alternately every two hours and the throat may be swabbed occasionally with a 1 per cent solution of mercurochrome-220. The local application of arsphenamin may be tried in throats from which the organisms of Vincent's angina are obtained. Details of symptomatic treatment may be found by consulting the appropriate sections of this work.

Convalescence as a rule is uneventful and directions to the patient during this period may depend upon symptomatic indications. Blood examinations should be made at intervals until the differential formula of the leukocytes has returned to the normal.

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CHAPTER XX

GLANDULAR FEVER

Allan Ramsey

Revised by George Blumer

This disease is an acute general infection of unknown origin. It was minutely described by Pfeiffer in 1889, since which time nothing new has been added to our knowledge of the subject. The disease is manifested by enlarged tender lymphatic glands, especially those of the cervical region, although the axillary and inguinal glands are very frequently involved, and it is highly probable that the bronchial and mesenteric groups are also affected. The constitutional disturbance in typical cases is considerable, there being high temperature, anorexia, and vomiting, and general malaise at the outset. All movements of the head become painful, and the neck is held more or less rigid, and on the second or third day the enlarged cervical glands can be felt.

The most marked feature in all the cases is the enlargement of the lymphatic glands. As a rule, the enlargement begins on the left side in the carotid region, and reaches full development by the end of the second to the fourth day. Generally a few hours before its completion on this side the beginning of swelling upon the right side can be noticed. Occasionally the swelling begins upon the right side, but it never begins simultaneously upon both sides. To the eye the swelling appears as a smooth elongated mass beginning at the angle of the jaw and extending downward and forward to a point somewhat beyond the middle of the jaw. The mass is about the thickness of the finger, and there is no matting together of the glands; three or four separate glands can readily be felt. They are always tender, often painful, and generally cause stiffness of the neck.

In 75 per cent of the cases reported by West there was also enlargement of the postcervical, axillary, and inguinal glands. They were not all enlarged in one and the same case, nor were they as tender as the cervical glands. He states, also, that in approximately half of his cases he could feel enlarged mesenteric glands; this has not been the experience of others, and yet, in view of the wide involvement of the lymphatic glands, it is highly probable that the mesenteric group is affected.

This disease occurs generally between the ages of three years and sixteen years, although cases occur occasionally in infants; in adults it is extremely rare. After the glands have become enlarged the diagnosis is comparatively simple.

There need be no confusion with mumps, because the parotid glands are not involved, and yet the swelling beginning upon the one side and later involving the other side gives the disease some resemblance to mumps.

As regards the origin of this disease, nothing definite is known. By some it is regarded as a streptococcic infection with the tonsils as the point of entrance, they showing at the time no apparent lesion. In nearly all cases of this disease there is a conspicuous absence of any tonsillar or pharyngeal inflammation. Upon this point there is general agreement. The constant presence of constipation led to the theory that the symptoms and adenitis might be due to infection from the intestine or to the absorption of toxins from the retained feces.

Prophylaxis.—In the matter of the prevention of this disease we are handicapped by our ignorance of its cause and of the special conditions which are favorable to its development. Fortunately the disease is not common and the number of cases developing at any one time is usually small.[1] An idea of the proportions of outbreaks may be gained from the fact that several reports consist of records of 5, 12, and 21 cases. West's large series of 96 cases is very unusual, but it included cases that occurred throughout a period of four years.

As regards contagiousness, Pfeiffer long ago pointed out the fact that the epidemic character of the disease seemed to be such as to confine it to a single house or family, beyond which it does not extend. There was no connection between the families affected; they lived far apart, were not acquainted with each other, nor had they been in communication with each other. Cases would spring up in portions of a city widely separated from each other; there was no appearance of house to house infection, nor were there any outbreaks in the schools to indicate the school as a source of infection or as a medium of transmission. In fact, all evidence of any regular method of spreading the disease was entirely absent. Therefore, it is apparent that any effort to close the schools when a few cases of glandular fever develop in a community is uncalled for, and as a prophylactic measure would accomplish nothing.

When the disease does appear in a family, however, it usually attacks two or more children of that family. West's 96 cases occurred in 43 families. Chapman reported that 5 of his own children contracted the disease, and, in 12 cases reported by Vipond, 4 were in one family.

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[1] According to Morse there was a mild but fairly widespread outbreak in this country during 1921.—Editor.

Prevention is, therefore, more a question of the individual family, and a child that contracts the disease should be isolated at once.

Isolation, to be successful, requires, among other things, early diagnosis; this, however, is usually easy of determination.

Treatment.—Most all of the cases are among children, and the digestive organs are decidedly disturbed from the onset. Until the initial vomiting is over, or nearly so, it is well to withhold all food and allow only water. When the vomiting has subsided the child should be placed upon the usual liquid diet of milk, broth, and soups. As soon as general improvement begins the diet should be increased without delay.

An initial purge should be given and the bowel thoroughly evacuated; if toxic material exists in the bowel, only good will be done by relieving it of this. It is well to give an occasional dose of calomel, and West states that he believes that the depression following the disease is not so great when calomel has been used. Nevertheless, he found that in several severe cases the use of calomel in an attempt to bring on a crisis invariably seemed to make more marked and longer continued the depression and anemia which always follow the disease.

There is no internal medication that has any marked effect upon the disease. Salol may be given in moderately large doses, and probably does good in some cases.

During the period of great discomfort and high temperature it is best to combine small doses of phenacetin with it. Salicin is said by some to relieve the symptoms considerably. Forchheimer states that in an epidemic connected with influenza he was able to shorten the course of the disease by the use of quinin.

Adenitis.—The pain in the neck may be greatly relieved by local applications. A cold compress or a small ice-bag over the affected glands is an excellent measure; cold bichlorid compresses, as advocated, probably owe their virtue to the fact that they are cold. Belladonna fomentations will often alleviate the pain, and I have used a 25 per cent ichthyol ointment to advantage in some cases. No local measures, however, will prevent the development of the adenitis upon the other side of the neck. Suppuration of the glands need not be feared, as this is an extremely rare event. Dawson Williams never saw it occur in any of his cases; it did not occur in West's series of 96 cases, and this has been the experience of many others; Schaeffer, however, saw it occur twice in 21 cases.

Complications.—Complications are to be treated according to their nature as they arise. The disease is singularly free from them, however. A few serious cases of acute nephritis have been observed, and epistaxis occasionally occurs. Among Chapman's own 5 children who had the disease, epistaxis occurred in all of them, and in 1 it was so severe as to be very alarming. The abdominal pain which occurs in so many of the cases is not so severe as to require any special measures. In some epidemics there are mild cases which run their course in two to four days, and require little or no treatment.

After severe cases there is marked depression, anemia, and frequently considerable loss in weight. During this period an ordinary tonic régime must be adopted, and some form of iron will usually be required. The enlargement of the glands usually disappears before the end of the third week, and chronic enlargement probably never occurs. Complete restoration to health frequently requires from four to six weeks from the beginning of convalescence.

Prognosis.—The prognosis is exceptionally good, death being a great rarity. In West's 96 cases there was but 1 death, and that occurred in a delicate child just convalescing from scarlet fever. In Seibert's 24 cases there was 1 death; in Vipond's series of 12 cases there was no mortality, nor were there any grave complications at any time.

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CHAPTER XXI

MILIARY FEVER

ALLAN RAMSEY

This is an epidemic infectious disease of unknown origin found almost exclusively in France, Germany, Austria, Italy, and England. It does not occur in this country, and at the present time it is found chiefly in France.

The treatment of the disease will be better appreciated if its salient features are borne in mind. It is characterized by profuse sweating, an erythematous and vesicular eruption, and by a group of nervous phenomena. The onset is usually abrupt, with fever, sweating, a sense of great oppression in the precordial or epigastric region, and prostration. This feeling of oppression or constriction is one of the most prominent symptoms, and seems to be purely nervous in character. At the end of the third day or upon the fourth the eruption appears, being first erythematous, and later becoming vesicular. It appears first upon the sides and back of the neck, and then gradually spreads over the entire body. With the appearance of the eruption there is a decrease in the constitutional disturbance, and the patient feels much relieved.

The sweating constitutes the most constant of all the symptoms, it appears at the beginning of the disease, and continues throughout its entire course. The sweats are profuse and continuous, and the patient is always wet with perspiration.

About the end of the second week or in the beginning of the third week the symptoms subside, and convalescence begins. The return to health, however, is quite slow; the loss in flesh has been marked, and convalescence finds a variety of sequelæ. Some patients have edema of the lower extremities; sometimes there are fibrillary twitchings of the face, and the tongue is tremulous; there may be persistent insomnia, anorexia, and profuse perspiration after the least fatigue; cardiac arrhythmia is also present at times. The slowness and complexity of the convalescence are quite characteristic of the disease, and this is true of mild attacks as well as of average ones. Several weeks are usually required for a restoration to health, and cases have been reported in which convalescence was prolonged for twelve months.

Miliary fever is a disease that presents a great variety in its gravity. In some epidemics there are scarcely any deaths, while in others the mortality is very high. The prognosis in general must, therefore, depend almost entirely upon the virulence which the disease displays in the epidemic that may be in existence at the time.

The mortality may differ in various localities during the same epidemic, as in that of 1887, when the different mortalities were 33 per cent, 1.33 per cent, and 0. In 1893 Schaeffer reported an extensive epidemic in Aussee in a population of 5,000, with no deaths. In 1852 there was an epidemic with a death-rate of 61.5 per cent. Given a severe epidemic with a high mortality, there is no symptom or condition upon which we can rely for a prognosis; under such circumstances one cannot even be sure of recovery in a mild case.

Prophylaxis.—A study of the frequency and character of the outbreaks of this disease in recent years seems to indicate that it is on the decline. This is in harmony with the general tendency of the checking of or decline of acute infections. Our knowledge of the various factors in the etiology and transmission of this disease is still quite meager; however, it seems to be established that those regions where the disease is endemic are damp, badly drained, or marshy. Improvements in sanitation and the drying and draining of the wet lands, both for hygienic reasons and for agricultural purposes, are probably responsible for this decline in the disease. Nevertheless, we must not forget that under the old bad sanitary conditions there were some long periods between epidemics, and the possibility of a recrudescence of the disease even under better sanitary conditions must be borne in mind.

During an actual outbreak of miliary fever the usual means of combating any contagious disease should be adopted. The patient must be isolated, his clothing and utensils disinfected, and the room must be disinfected when the disease is over. It is interesting to note that Brouardel, in an extensive epidemic thirty-seven years ago, organized a disinfecting corps which attempted wholesale disinfection by means of steam. How long a convalescent patient is capable of infecting others is not as yet known. If more were known of the method of transmission of miliary fever, it might be possible to take much more effective measures for its complete eradication.

Treatment.—Formerly it was a popular idea among the laity, and especially with the peasantry, that it was injurious to the patient to remove his wet clothing. Instead, his sweating was increased by adding much extra bed covering, and by excluding all fresh air by keeping both doors and windows closed, and by plying him at the same time with hot aromatic drinks. This is supposed by some of the French physicians to have been the cause of many deaths.

In the absence of any specific medication the treatment is largely that of any severe infection with marked febrile and constitutional disturbance. An abundance of fresh air should be supplied, the patient's gown should be frequently changed and a dry one put on, and the body should be sponged once or twice a day to remove all traces of perspiration and keep the patient free from odor. The diet and care of the bowels are to be regulated as in any acute febrile condition.

In many of the epidemics of this century quinin was used and was very well thought of. During the extensive epidemic of 1887 it, however, does not seem to have been used; in that epidemic hydrotherapeutic measures were employed for high temperatures, and an expectant line of treatment was adopted. For the intense nervousness in the early part of the disease sedatives may be used.

Relapses, which are very frequent in some epidemics, are to be treated like the original attacks. A relapse is seldom fatal.

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CHAPTER XXII

TRENCH FEVER

Homer F. Swift

Synonyms.—Trench fever: five-day fever, quintan fever, Volhynian fever. During the War this malady received many other names derived either from the most pronounced symptoms or from the locality in which the first cases were noted.

Historical.—Although scattered references to conditions resembling trench fever can be found in older literature, practically all of our definite knowledge concerning this disease was obtained during the World War. Often confused with influenza and also called "pyrexia of undetermined origin," trench fever doubtless existed along with typhus as an endemic disease in Russia where it was first described by Austrian army medical officers among their troops taking part in the early invasion of Galicia and Volhynia. German troops on the Russian front soon contracted it; and probably soldiers of the Central Powers served as carriers of the infection to all military fronts whence it was disseminated to the lines of communication and military centers in the rear. Although some cases developed among civilians, it is noteworthy that by far the majority of individuals infected were connected with the armies. Following the armistice and the placing of the soldiers in permanent, louse-free quarters there was a rapid falling off in the incidence of new cases. Many patients with chronic forms of trench fever were cared for in military hospitals or invalided out of the armies. These patients are the chief concern of physicians in private practice, not only because of their invalidism, but also because of the possibility of their becoming a source of infection if infested with lice.

While the official records of the American army show only a few hundred cases of this disease to have been recognized, the incidence was doubtless many times greater. The majority of the reported cases in the American Expeditionary Forces were from the Third Army, where the medical officers were especially instructed in the diagnosis of trench fever. It is highly probable that the disease was as prevalent among the divisions comprising the other two armies, but that it was confused with influenza which was very common at that time; the two diseases are often indistinguishable unless the patients are very carefully studied over relatively long periods.

Since the close of the War the civilian populations of America, Austria, England, France, and Germany have been practically free from trench fever; but the louse-infested countries belonging to the former Russian Empire doubtless continue to furnish many cases of this fever, as well as of typhus. This view is corroborated by the experience of the International Red Cross Typhus Fever Commission which found both conditions prevalent in Poland. It is interesting to note that both are spread by insect vectors—usually body lice—and are also intimately associated with the presence of the so-called Rickettsia bodies in these insects.

Trench fever was accurately described by medical officers in various armies. Two commissions, one English, the other American, added much to the exact knowledge of the mode of transmission and the nature of the virus. The clinical material furnished by the volunteers who submitted to inoculation permitted us to learn more definitely the wide variations in different cases; and from these patients it was possible to infect lice so that the nature of the virus and the relation of the infectiousness of the lice to the appearance of Rickettsia bodies could be more accurately determined. The original description of Rickettsia bodies in infected lice was made by German army medical officers.

Definition.—Trench fever is a specific infectious disease, characterized by an acute onset with pyrexia and marked general toxic symptoms, by pain involving exposed periosteal surfaces, tendinous and aponeurotic attachments, by conjunctival congestion, transitory macular eruption and enlarged spleen. There is a marked tendency for the symptoms and signs to disappear and recur at more or less regular intervals, although in some instances there is a continuous course. Occasionally trench fever becomes chronic when the outstanding symptoms are neurasthenia and an abnormal condition of the circulatory system, variously designated as "effort syndrome," or "disordered action of the heart." The infectious agent is usually transmitted by the body louse, although the urine of patients may contain the virus and induce an attack of the disease if brought into contact with excoriated skin.

As the temperature curves are the most tangible objective evidence of infection, the different types of cases have been classified according to their fevers. Few diseases present more widely diversified fevers; and our experimentally infected patients proved that all types may arise from the successive inoculation of different individuals with the same strain of virus. The various types of temperature curves may be divided roughly into two groups: (1) continuous; (2) relapsing. Under 1 we have: (*a*) short influenzalike form with fever lasting one to six days; and (*b*) long, typhoid, or septic form with fever lasting from a week to a month or more. Under 2 may be placed all forms in which relapse is the outstanding feature: (*c*) two cycles of three or four days fever with an intervening afebrile period of about twenty-four hours; (*d*) several cycles of fever with each cycle beginning every five or six days and lasting two to four days; (*e*) individual bouts of fever lasting twenty-four to thirty-six hours with relapses occurring every five or six days. Not infrequently combinations of forms *d* and *e* are seen in the same case; cases are also seen in which, at the time of an expected relapse, there is no fever but increased pulse rate and other symptoms of a relapse. Finally, a certain number of patients have long-continued, low-grade fever with free intervals following no particular course.

The pulse rate usually parallels the temperature curve for the first three weeks; then, if the patient has not overcome the infection, it becomes more rapid, and attacks of tachycardia occur at irregular intervals; or the rate may be continuously high, with accompanying symptoms of precordial pain, palpitation, and weakness. This state of affairs may persist for months, even years; the British Commission has shown that such patients are carrying the virus—a proof that they are still suffering from an active chronic infection.

It is convenient to discuss the other symptoms in connection with the pyrexia. The onset is usually acute with marked prostration, headache, especially postocular and temporal, pain in the back, in the extremities, and at times in the abdomen; often dryness of the pharynx and slight, dry cough. Usually there is transitory conjunctival congestion and pain on rotating the eyeballs; also a moderate number of red macules over the abdomen which disappear completely on pressure. In one-fourth of our patients a moderately enlarged spleen with a firm sharp edge was found the first day; and in two-thirds of them by the fifth day. Most patients have a palpable spleen some time during their infection; in some for only a few days, in others persistently. According to many German observers there is frequently a similar enlargement of the liver; but in our experience this was rare.

Early in the disease many patients complain of urinary frequency without any objective manifestations to explain it. Transitory febrile albuminuria is not infrequent. Aside from febrile anorexia, no characteristic gastro-intestinal symptoms are present.

Pain and tenderness in the shins are outstanding features in many patients; but systematic examination often reveals similar pains in other regions, especially in the back. The severe shin pains and "rheumatic pains" about the joints often are not noted until the second week and may thereafter recur daily or be present only with each febrile relapse. When present daily they usually appear in the late afternoon and persist during the night; they cause much of the insomnia that is so prominent a feature in many cases. Tenderness on pressure over superficial bony prominences can be easily elicited in most patients complaining of pain;

tenderness is also often found by exerting pressure over such regions as the fascia lata femoris. Abdominal pain simulating that of appendicitis, but usually bilateral, is found early in many patients. Insomnia, early toxic in origin, later due to pain, is often a marked and troublesome symptom.

Moderate leukocytosis with a relative increase in polymorphonuclear leukocytes is usually found with the early bouts of fever; occasionally there is marked leukopenia. Later, in the subacute or chronic forms of the disease, there is a relative increase in mononuclear cells.

Because of the non-fatal character of the infection, the only histopathological changes that have been reported are in the macules, where in the hyperemic and edematous corium there is a perivascular infiltration of lymphocytes mixed with some polymorphonuclear leukocytes.

Mode of Transmission and Prophylaxis.—The disease is due to a specific etiologic agent that behaves in the presence of various physical and chemical environments in a manner similar to that of many filter-passing microörganisms. It is found occasionally in the sputum of patients, often in the urine, and always in the blood at some stage of the disease. It is also found in the bodies and excrement of body lice that have fed several times upon trench fever patients, but does not appear until an interval of from five to ten days following the infecting feed, and then persists until the death of the lice. There is a remarkable coincidence between the infectivity of louse excrement and the appearance of Rickettsia bodies in this material.

Although men may be infected simply by the bites of the infected lice, they are more surely infected by applying the excrement of such lice to their scarified skin. It is important to recognize the latter possibility, for clothing and other material containing infected louse feces may still be a source of danger even though louse-free. Lice may be eradicated from clothing by dry heat at 60° C.; but exposure to moist heat of at least 70° C. is necessary to kill the virus. The infectious agent can survive several months in dried excrement from lice.

Diagnosis.—Trench fever must be differentiated from influenza, typhoid and paratyphoid, malaria, spirochetal relapsing fever, dengue, typhus, and epidemic jaundice (Weil's disease). These diseases are distinguished by certain positive findings peculiar to each condition; often it is necessary to follow and record accurately the symptoms and signs in a trench fever patient for a week or ten days before a correct diagnosis is possible. The relapsing character of the symptoms in the first weeks, the peculiar hardness of the spleen, the characteristic macular rash recurring with each relapse and the extremely annoying shin pains are all helpful in establishing diagnosis. The diagnosis in the chronic form of the disease rests upon the history of the characteristic relapsing symptoms at the onset, and a clinical picture of neurasthenia, a rapid, irritable heart

—especially after slight exertion—and a persistent loss of weight, or failure to regain weight lost at the beginning. The development of Rickettsia bodies in the excreta of normal lice that had fed upon a patient suspected of having a chronic trench fever would be strongly confirmatory evidence.

Prognosis.—No fatal cases of trench fever have been recorded. From 85 to 90 per cent recover completely within two months. About 5 per cent have persistent symptoms and the condition called disordered action of the heart. In our experience, men under thirty-five years of age recovered more quickly than did older individuals. Patients with severe symptoms and high fever in the first two weeks seemed to develop an immunity more rapidly than did those individuals with indefinite symptoms and low-grade fever.

It is difficult to be certain when a patient is completely free from the disease. Recently I have seen soliders infected in 1918 who were still having periods of illness unexplainable on any other basis than that of relapses of trench fever.

Treatment.—There is no known specific treatment for the disease; hence therapy must be largely symptomatic. The recovery of a patient depends upon the development of an immunity which is more or less transitory. All therapeutic measures usually employed to help a person develop his resisting power to the highest degree should be applied, not only during the febrile periods, but between them. Most important are rest, attention to nutrition, and, finally, proper exercise. The weight curve is a fair index of the progress of the disease. Except when having high fever the patients are able to assimilate good amounts of easily digested food; in the chronic stages it may be necessary to cater to a capricious appetite.

Because of pain and insomnia the securing of rest is more difficult than in many other diseases. At the onset and during the acute relapses the patient willingly follows the doctor's directions to remain in bed; between relapses he often feels well enough to attempt almost any exertion. It is advisable, however, for him to remain in bed until the probability of a relapse has passed. Then he should be gotten up slowly with a constant ookout for a relapse which is not infrequently induced by exertion. Undue or prolonged increase in the pulse rate indicates slow convalescence. After the patient is able to be up all day without discomfort, he should undergo a course of graded exercises until he has reached the point where he is able to resume his usual activities. During this course he should be carefully watched for relapses, for in our experience it was a common occurrence for them to follow unusual exertion on the part of the convalescent. When relapses occur it is necessary for the patient to return to his bed and resume a slower convalescent régime.

Certain drugs are of value in relieving the pains. We found aspirin and phenacetin 0.3 gm. (gr. v) to be effective in the majority of cases.

This can be repeated two or three times a day if necessary. When this did not control the pains, the addition of codein to the mixture afforded relief to most patients. Rarely was it necessary to resort to the use of opium or morphin, although many English and German medical officers state that these drugs were needed in the most severe cases. Pyramidon, 0.3 to 0.6 gm. (gr. v to x), is very effective in alleviating the "neuralgic" pains and headache. When the patients begin to get out of bed it is often useful to give a bitter tonic containing nux vomica. For the insomnia occurring early, the sedatives already mentioned are the most effective; for that occurring later, a combination of aspirin and veronal is often useful. Hydrotherapeutic sedative measures are also of benefit at this time.

Numerous forms of non-specific protein therapy and intravenous injections of colloidal substances were tried during the War by various observers in an attempt to cut short the course of the disease. It is difficult to estimate the true value of any therapeutic measure of this kind because of the great variation in the clinical picture in untreated patients. From the observation that those patients having severe symptoms and high fever early usually recovered more rapidly and completely than those failing to react violently, it might be assumed that the induction in the latter type of individuals of the well-known fever and leukocytic reaction so characteristic of non-specific protein therapy would result in a rapid cure. Richter, and Sweet and Wilmer, indeed, report rapid recovery of fair-sized series of patients who received intravenous injections of 10 c.c. of 1 per cent collargol every two or three days. If patients with the chronic disease are encountered who fail to respond to more general measures it might be of value to try this treatment.

Patients with the chronic forms of the disease must be treated from the point of view of undernourished, nervous, chronically poisoned individuals. Here special care must be given to feeding the patient sufficient calories in properly distributed food to help him regain his lost weight. When he is afebrile for two or three weeks, graded exercise is most useful. Hydrotherapy or change of climate to that found most beneficial for tuberculosis patients is often of value. These patients are often of the neuropathic type, normally easily discouraged; hence it is important to apply proper psychotherapeutic measures. Exercise in the form of games is frequently of benefit, but it must be regulated and controlled. Byam states that the administration of thyroid extract in small doses is often helpful in cases of this type. He also recommends atropin beginning with 1/300 gr. and increasing the dose until a steadying effect on the pulse is obtained. We have had no experience with either of these preparations in the treatment of this condition, so are unable to make definite statements as to their efficacy.

THE MYCOSES

CHAPTER XXIII

ACTINOMYCOSIS

LLOYD W. KETRON

Actinomycosis is a chronic infection due to a special type of fungus, Actinomyces bovis, which attacks by preference connective tissue but which may involve other tissues or organic structures of the body. It is characterized by the formation of localized areas of connective and granulation tissue enclosing multiple abscesses. In the purulent material from these abscesses the causative organism is found in small masses resembling sulphur granules. The disease is widely distributed and is more apt to affect adult males. It is somewhat uncommon but not rare.

Symptomatology.—According to its location in the body the disease is usually described under the following varieties.

Cervicofacial Actinomycosis.—This form includes more than one-half of all cases. Infection takes place through the mucous membrane of the pharynx and mouth or, probably in the majority of cases, around carious teeth, particularly those of the lower jaw. Toothache and various dental affections frequently precede the development of the disease. The process extends through the jaw or directly into the soft tissues of the face and neck with the formation of circumscribed nodules or infiltrated masses in the subcutaneous tissues. Painful subperiosteal swellings may occur around the teeth and occasionally ulcerating nodules on the tongue. As the disease progresses, multiple abscess formation occurs and discharging sinuses appear on the surface. The overlying skin may assume a dark red or purplish color and have a lumpy uneven surface. As a result of the extensive connective-tissue proliferation, the whole affected area has a "wooden" induration, which usually extends considerably beyond the areas of apparent suppuration. Extension may take place to the brain, bones of the skull and meninges. The general health is not usually affected so long as the disease remains localized in the face and neck areas. Pain is not a prominent symptom but may be present particularly after secondary infection has taken place. Trismus often occurs when the muscles of mastication are affected. The lymphatic glands are usually not implicated.

Thoracic Actinomycosis.—Primary infection takes place in the lungs, usually through inhalation of the fungus on particles of dust. The physical signs are those of bronchitis, pulmonary infiltration and abscess formation. The condition suggests tuberculosis with the exception that the bases of the lungs are usually first involved. There is cough with a mucopurulent and frequently bloody sputum. Involvement of the pleura gives rise to signs of pleuritis and frequently of encapsulated fluid. There may be retraction of the chest wall with limitation of motion and dislocation of the heart. After the disease has reached the pleura, it usually rapidly involves the thoracic wall, extending through the muscles to the subcutaneous tissues where it produces localized areas of induration with suppurative foci and sinus formation. After a time there ensues loss of strength, anemia, night sweats, dyspnea and usually slight fever. The esophagus may occasionally be involved, which may cause pain and difficulty in swallowing. Extension to the heart and pericardium may occur.

Abdominal Actinomycosis.—In this form of the disease the portal of entry is through the intestinal tract, although occasionally infection may take place by metastasis or extension from the chest. The earliest signs are usually in the ileocecal region and are associated with the development of an indistinct, irregular mass which is not usually painful and shows no characteristic features. This may be the first manifestation of the disease, or it may be preceded or accompanied by fever, chills, night sweats, intestinal colic and vomiting. The mass, however, may appear in other localities but eventually extension takes place into the abdominal wall with abscess and sinus formation. Jaundice may be present from involvement of the liver, and cystitis and pyelonephritis from involvement of the urinary tract. According to Wright, the disease may simulate appendicitis, typhoid fever, carcinoma of the intestines, tuberculosis of the ileocecal lymph-nodes, abscess of the liver, psoas abscess and sarcoma of the iliac bone.

If the process becomes widely disseminated, the symptoms are those of pyemia. Involvement of the central nervous system with its special symptomatology occasionally occurs through a general metastasis or extension from other tissues.

Cutaneous Actinomycosis.—Sometimes the skin is primarily involved from direct inoculation with the organism. Pels has reported a case following the application of chewing tobacco to a wound on the hand. Nodular infiltration with multiple abscesses and ulcers characterize this form of the disease and demonstration of the actinomyces in the pus is necessary for a diagnosis.

Etiology and Pathology.—The disease is due to a fungus, the Actinomyces bovis, which also produces the condition in cattle known as "lumpy jaw." It was discovered in the ox in 1877 by Bollinger and Hartz and in the following year by Israel and Wolf in human beings. It is found in the pus from diseased tissue in the form of characteristic yellowish granules which average the size of a pinhead. Microscopically, these small bodies are seen to be composed of a central mass of interlacing filaments or coccuslike bodies from which radiate slender, branched or unbranched, threads which show characteristic bulbous or clublike terminations. Considerable variation in the cultural characteristics of the organisms obtained from cases of actinomycosis has led to confusion in attempts to establish a specific variety as the sole cause of the disease. The two main forms which have received the most consideration are: (1) an aërobic organism described by Boström and others, which is easily grown on artificial media and has a wide distribution in nature; and (2) an anaërobic variety described by Wolf and Israel, which is grown with difficulty and is thought to be restricted in existence to the animal body. The latter organism has been accepted by the majority of investigators as the cause of the disease.

Infection is generally assumed to take place through injuries to the mucous membranes caused by the chewing of grains, straw, grasses or other dry vegetable matter, and the occasional finding of foreign material of this character in actinomycotic lesions has supported this view. Wright, however, believes that the organism is not carried through these media but that it exists as a saprophyte in the mouth and gastro-intestinal tract and that foreign substances merely cause the injuries through which the fungus gains entrance to the body. His idea is supported by the investigations of Lord, who was able to produce omental tumors in guinea pigs by intraperitoneal injections of material from tonsillar crypts and carious teeth of persons free from actinomycosis. These tumors were histologically identical with actinomycotic lesions and showed the typical clubbearing granules.

There is little evidence that the disease is ever transmitted directly from animal to man and only a few instances of apparent infection from man to man have been observed. Isolated foci containing the fungus can be produced by experimental inoculation of animals, but the progressive lesions as observed in man and cattle have not been reproduced successfully.

The disease extends principally by continuity, having a predilection for connective tissue, although other tissues and structures may be involved. Extensive proliferation of connective and granulation tissue with multiple abscess formation is the most prominent pathological feature. The affected structures may have a honeycombed appearance due to numerous communicating channels, and large encapsulated abscesses may occur. The disease is never disseminated by the lymphatics, and the lymphatic glands show a remarkable immunity to involvement. Dissemination may occasionally occur through rupture of a suppurating focus into the blood-stream.

Treatment.—The prognosis is good in cervicofacial actinomycosis or when the lesion is localized primarily in the skin, but the outcome is very unfavorable in the thoracic and abdominal varieties, most of the cases ending fatally.

The principal therapeutic procedure consists in the administration of potassium iodid internally and surgical measures locally. There has been a wide variation of opinion, however, as to the value of potassium iodid, some doubting that it exerts any beneficial effect on the course of the disease, while others acclaim it as a specific. This contradiction of ideas is due, partly at least, to the fact that many cases of the cervicofacial variety will heal after local surgical measures alone if efficient drainage has been established. In the majority of instances, however, the drug has seemed to exert a beneficial effect on the disease, not directly by destroying the parasite—some experiments in vitro show that it has very little fungicidal action—but in causing a softening and breaking down of the lesions with the mechanical extrusion of the fungus.

The dosage of potassium iodid which has been recommended for internal administration has varied from 30 to as much as 150 drops of a saturated solution thrice daily. Mattson gives as the initial dose 75 drops three times a day and increases it by 1 drop daily until 125 to 150 drops are reached. If symptoms of iodism intervene, the drug should be stopped for three or four days, but later should be resumed at the same dosage as when it was discontinued. Some authors prefer maximal doses with intermissions of three or four days at the end of each week of administration.

Copper sulphate has been used internally by Bevan in a certain number of cases with apparently good results. He gave from ¼ to ⅛ gr. three times daily. It is certainly not as effective as potassium iodid.

Based on the high fungicidal property of methylene-blue for actinomyces in vitro, Jensen and Schery used it internally in the treatment of one case of cervicofacial actinomycosis. The patient was cured but, since X-ray treatments were also given at the same time, it is impossible to estimate the share in the result which should be apportioned to the methylene-blue.

Tuberculin has been used successfully in the treatment of one case of the abdominal type of the disease by Maier, who also refers to a similar case reported by Billroth. The number of cases treated, however, has not been sufficient to establish the value of the procedure.

Various preparations have been used for *local injections* into the diseased tissues, for the purpose of breaking down the tissues and destroying the organism in situ. Among these may be mentioned solutions of 5 per cent potassium permanganate, 5 per cent phenol, 3 to 5 per cent silver nitrate and 1 to 5 per cent potassium iodid.

Copper sulphate has also been recommended and Baracz has recently reported excellent results from the use of this drug in 30 cases. The concentration of the solution varied from 0.25 per cent to 2 per cent, the higher concentrations being used when only small quantities were required. The abscesses were opened, fistulæ were curetted, sinuses and open cavities were cauterized with iodin, after which compresses of aluminum acetate or copper sulphate solution were applied. Final healing was hastened by the use of the silver nitrate stick. Most of these procedures give rise to somewhat intense local reactions and should not be repeated until these have disappeared.

Local surgical methods are of great importance no matter what other means of treatment may be instituted. Total excision of the affected area is seldom possible and should not be attempted unless the diseased focus is small. All suppurating cavities should be opened with one or more incisions so that thorough drainage can be assured. Sinuses and fistulous openings shoud be curetted and cauterized with iodin or phenol. Colebrook believes that prompt incision, with drainage of all areas of softening, is of paramount importance as a check to the progress of the infection, inasmuch as the fungus will propagate in the fluid of an abscess cavity but cannot do so in unaltered lymph. He emphasizes the importance of removing diseased tissue with a dry gauze swab in place of the usual sharp curet which opens up healthy tissue to infection.

Vaccine therapy has been used with success by Malcolm, Dean and others and has been particularly investigated recently by Colebrook who treated 23 cases in this way. The dose varied from 5,000,000 to 10,000,000 mycelial fragments given at intervals of five days, and both autogenous and stock vaccines were used. The injections caused no reactions except for an occasional rise in temperature. Colebrook concludes that the treatment of actinomycosis with vaccines facilitates recovery when efficient surgical drainage of the affected tissue is secured and maintained.

The *X-ray* has frequently been recommended in treating the disease, and Mattson has found it of value as an adjunct to the medical and surgical treatments. Bevan believed it to be especially valuable when combined with the internal administration of potassium iodid, since he was able to show experimentally that free iodin was liberated from solutions of potassium iodid under the influence of X-ray radiation. Heyerdahl reports the cure of a number of cases with radium.

Most methods of treatment are of value only in the cervicofacial type of the disease or when the skin is primarily involved. In the abdominal and thoracic forms very little can be done. Operative measures may be helpful when the disease involves the pleura or is restricted in the abdomen.

Sawyers reports the cure of a patient with pulmonary involvement by the injection of a 1 per cent solution of potassium iodid directly into the lung tissue, and one of Baracz's patients showed great improvement after injections of copper sulphate into the diseased lung.

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CHAPTER XXIV

STREPTOTHRICOSIS

Lloyd W. Ketron

Under this heading is included a group of infections due to various forms of streptothrix organisms, exclusive, however, of the variety caused by the Actinomyces bovis—known also as Streptothrix bovis communis—which, because of special characteristics, is usually described separately under the title of "actinomycosis." These organisms are apt to invade various organs and tissues of the body but the lungs usually bear the brunt of the attack. The disease is rare.

Symptomatology.—Streptothricosis of the lungs usually gives a clinical picture resembling that of tuberculosis or thoracic actinomycosis. Cough, with mucopurulent sputum, irregular fever, emaciation and loss of strength are the prominent symptoms. Abscess of the lung and empyema may occur and the disease may extend through the chest wall with the formation of fistulæ. Dissemination frequently takes place and metastatic lesions are found in the abdominal viscera, subcutaneous tissues and brain.

Schottmüller has reported a case of a streptothrical sepsis following a rat bite. There was pain in the legs and arms, fever, bronchitis and a macular eruption on the skin. The organism was obtained from cultures of the blood.

Primary infection of the brain with abscess formation occurred in 2 cases reported by MacKee, and primary meningeal infection with pulmonary embolic abscesses has been recorded by Bell.

The disease has occasionally been found limited to the skin and subcutaneous tissues. In Guy's patient only the hand and arm were implicated and, clinically, the infection resembled sporotrichosis. Unna also refers to a case with nodular lesions in the submaxillary and submental regions clinically similar to actinomycosis of this region.

Streptothrical forms have at times been recovered from eye infections.

Etiology.—Several varieties of streptothrix have been described as causing the disease in man. Considerable confusion has also resulted in the nomenclature, since some authors prefer the name "actinomyces" for the genus, whereas others have used the terms "cladothrix," "oöspora" and "nocardia." The organisms occur as true branching, spore-bearing, fine mycelia and differ from the Actinomyces bovis in that they do not form the radiating wreathlike forms so characteristic of actinomycosis. The "sulphur bodies" of the latter disease are also not usually present in the streptothricoses, although Glaser and Hart have recently reported a case in which granular masses of this character were found.

Streptothrical forms are widely distributed in nature, and infection in man occurs probably in the majority of instances through the lungs.

Treatment.—The prognosis depends upon the severity and extent of the infection. Most of the cases with involvement of the lungs or brain have proved fatal. Schottmüller's patient, however, who had a streptothrix sepsis, recovered and Meyer reports a case of a streptothrix empyema which was cured by operation. Bloomfield and Bayne-Jones' patient apparently recovered after the opening and draining of a solitary liver abscess. This patient had also a lung infection, since the organism was found in the sputum and there were some changes at the right base. He admitted that he had had a slight cough off and on with some lumpy sputum for some two years, but the disease had apparently given him but little trouble. It is quite likely that mild lung infections of this character occur not infrequently and end in recovery or become arrested. Treatment would be according to the general principles appropriate for tuberculosis.

Potassium iodid and vaccine injections have apparently been of little or no value, although, in Guy's case, the infection of the hand and arm healed rapidly following the administration of potassium iodid.

Petruschky reports good results in 2 cases from the use of a preparation analogous to tuberculin which he calls "streptotrichin."

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CHAPTER XXV

SPOROTRICHOSIS

Lloyd W. Ketron

Sporotrichosis is a chronic infection, usually limited to the skin or subcutaneous tissues, but which may involve any tissue of the body. It is due to a spore-bearing fungus and is characterized by the development primarily of individual nodules resembling syphilitic gummata which later result in abscesses and ulcers. The diagnosis rests on the demonstration of the fungus in the affected tissues and the disease usually responds rapidly to potassium iodid therapy.

The condition is rare but has a wide distribution and reports of cases have come from many countries. In the United States the majority have been found in the Mississippi basin. Adult males form the majority of sufferers but no age is exempt.

Symptomatology.—Two principal forms are recognized on the skin: (1) the lymphangitic or localized variety; and (2) the disseminated, gummatous variety.

Lymphangitic Sporotrichosis.—This is the variety usually met with in the United States. It results from the inoculation of the organism directly into the skin through some injury, often quite trivial, such as a small puncture wound. The exposed parts, especially the hands and arms, are most frequently affected, although the initial lesion may occur on any part of the body. At the site of inoculation an indurated ulcer—the so-called sporotrichal chancre—often develops, although frequently the point of entrance of the organism is not discoverable. Some weeks later one or more small subcutaneous nodules appear in a line up the arm or leg, following the course of the lymphatics draining the affected area. The lymphatics themselves are usually inflamed and form hard cords connecting the nodules. At some time later the lesions undergo central softening and rupture on the surface, with a formation of fistulous openings or ulcerations. The lymphatic glands draining the affected area may or may not be enlarged. When the primary infection is on the face, the lesions often resemble verrucose or papilliform tuberculosis. The lymphangitic form of the disease rarely becomes disseminated.

Disseminated Gummatous Sporotrichosis.—This variety has been most frequently observed in France. It is not limited in extension to a chain of lymphatics but may be disseminated over the entire body. The lesions usually number from four to thirty-five, but a hundred or more have been noted. Small nodules develop in the subcutaneous tissues which are hard, elastic, painless and freely movable. As they grow larger, there ensues a softening in the center with the development of a "cold abscess." In some cases the abscesses remain indolent indefinitely, showing little tendency to ulcerate. In other cases there is more or less rapid destruction of the overlying skin with the formation of narrow fistulous openings or ulcerations from which exudes a viscid, colorless or reddish pus or a yellowish serous fluid secretion. The ulcerations usually resemble those of tuberculosis with undermined, irregular edges, but sometimes ecthymatous or rupial forms may be observed. In fact a great variety of lesions have been described but, according to de Beurmann, the gumma is always the fundamental manifestation. Spontaneous healing is slow and inconstant. The lymph glands are not usually enlarged.

De Beurmann gives the following characteristic points of the disease:

> "The large number of lesions contrasting with the preservation of a good general state of health. Partial cup-shape softening of a node, which is at first indurated, and the center of which breaks down. Slight ulceration, which enlarges secondarily. Irregular and violaceous edges, almost always undermined, covering subcutaneous recesses in which pus accumulates. The contrast between the small area of ulceration and the size of the gumma from which it arises. The coexistence of several contiguous ulcerations, separated by a slender bridge of violaceous skin, over one and the same gumma. Viscous pus or lemon yellow viscous discharge. The ease with which auto-inoculation occurs. 'Cold' and indolent evolution. The cicatrization of the skin in spite of the persistence of an abscess under the cicatrix. Smooth elastic cicatrices, with irregular edges and often with denticulation of badly attached cutaneous tags surrounded by a brown pigmented area. The constant absence of enlarged glands."

The extracutaneous lesions of sporotrichosis may be isolated, but they nearly always occur associated with skin lesions. Although the disease apparently does not become systemic, it has been found to attack almost all the tissues of the body. Gummata may develop in the muscles and there may be osteoperiostitis or osteomyelitis. De Beurmann has seen an intra-osseus abscess as the sole manifestation of the disease. Synovitis or osteo-arthritis may be present. The eye is often implicated. Intra-ocular lesions may occur in the disseminated form of the disease and primary infection of the conjunctiva or lacrimal sac has been observed.

Sporotrichotic orchiepididymitis has been noted and a pyelonephritis from which the organism was recovered was reported in one case. There may be ulcerations or papillomatous vegetations in the mouth, throat and on the larynx.

Although sporotrichosis usually causes a very mild general reaction, or none at all, in exceptional cases it may assume the characteristics of an acute infection with fever, chills and nausea. It then resembles a coccal septicemia with skin metastases. The lung may occasionally be involved. Warfield has recently reported a case of disseminated gummatous sporotrichosis which resulted in death. Beside the severe cutaneous ulcerations a small nodule was found in the lung which was proved culturally and histologically to be of sporotrichotic origin.

Etiology and Pathology.—The disease is caused by a fungus, the sporotrichum, which is easily cultivated on artificial media, on which it forms a fine mycelium with small round or oval spores. It is very difficult to demonstrate in pus or diseased tissue and for diagnostic purposes cultural methods must be resorted to. The organism was discovered by Schenck in 1896 in an ulceration of the hand and was given the name of Sporotrichum schenckii. Later de Beurmann and his associates reported a number of cases and it is especially due to their extensive studies that the disease has become generally recognized and its important manifestations established. In France the organism is usually known as Sporotrichum beurmanni, which some authors think is identical with the Schenck variety. Other pathogenic varieties have also been described. The fungus apparently is widely distributed, growing as a saprophyte on vegetables, fruits, decaying materials and in the soil. It has also been found on various insects and it is possible that the disease may sometimes result from their bites or stings. A small wound with an object contaminated with the organisms, or contamination of the site of injury, permits the entrance of the fungus into the skin, which gives rise usually to the lymphangitic form of the disease. In the disseminated variety the point of entrance is probably through the mucous membrane of the mouth, throat or intestinal tract. De Beurmann and his associates have been able to infect animals by feeding them on milk infected with the organism.

Sporotrichosis occurs spontaneously in some animals, especially the horse, in the United States. According to Meyer, however, it is rarely transferred to man by infected animals. They more probably act as passive carriers, as they can harbor the organisms in a saprophytic state in their mouths. The fungus has been isolated from the blood of man infected with the disease and also from the sputum. In the latter case, however, its presence does not necessarily indicate infection, inasmuch as it may denote a saprophytic existence in the mouth or probably may be due to some contaminated food recently eaten.

The disease may be produced experimentally in various animals, the rat being especially susceptible.

Microscopically the lesions may resemble those of tuberculosis, syphilis or chronic suppuration. A typical nodule, according to de Beurmann, consists of a central abscess containing polymorphonuclear leukocytes and macrophages, an intermediate zone containing degenerated epithelioid giant cells and tubercular follicles, and, at the periphery, a proliferation of basophile lymph and connective tissue cells or a fibrocellular infiltration.

Prognosis and Treatment.—The disease rarely causes death but shows little tendency to heal unless treatment is instituted. Potassium iodid is a specific and when given in proper doses rarely fails to bring about a rapid disappearance of the lesions. The exceptions to this rule, according to de Beurmann, are when there is involvement of the upper air passages and of the mucous membrane of the pharynx, or where the organism develops on cachectic soil, particularly in the tuberculous and in patients who do not tolerate an iodid therapy.

Potassium iodid should be given in increasing doses up to a dram or more three times a day. If it is not well tolerated, the various special combinations of iodin on the market, for which a less irritating effect is claimed, may be tried. The experimental work of Davis indicates that potassium iodid has very little germicidal action on the sporotrichum itself, although causing rapid disappearance of the lesions. Outside of the body the fungus will live forty-eight hours in a 10 per cent solution of potassium iodid, and in a 1 per cent solution, which is far above its concentration in the tissues of the body when given therapeutically, no effect was seen after seventy-four days. Administration of the drug to rats eight days before inoculation with sporotrichosis, or a week after, did not prevent the development of the disease.

Local measures, such as incision and curetting, are apparently of no value and may be harmful. It is usually recommended that open lesions be washed with a weak iodin or potassium iodid solution. The following formula is frequently used. Potassium iodid 10 gm., iodin 1 gm., water 500 c.c.

Treatment with potassium iodid has been so uniformly successful that apparently few other methods have been tried.

X-ray would undoubtedly hasten the absorption of the lesions. According to MacKee, it has been used successfully by Shelmire and Crutchfield without the administration of the potassium iodid. Its value, however, would be limited to the individual lesions treated and it should be used only as an adjunct to potassium iodid therapy.

Hecht caused healing of the lesions by the administration of a vaccine made from cultures of the organism, and this method is worthy of trial in cases which may be especially resistant to the usual forms of treatment.

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CHAPTER XXVI

BLASTOMYCOSIS

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Synonyms.—Saccharomycosis hominis, blastomycetic dermatitis, oïdiomycosis.

Blastomycosis is a chronic, infectious disease, due to a budding fungus, which is limited to the skin in the majority of cases but which may become systemic, involving a great many of the organs and tissues of the body. In the systemic form abscesses of various sizes or proliferative nodules develop in the diseased tissues. When the skin alone is affected, slowly spreading, chronic inflammatory patches are found, characterized by a warty or papillomatous surface from which small droplets of pus frequently containing the causative organism, can usually be expressed.

The majority of the cases first reported were from the neighborhood of Chicago, but the disease has been recognized as occurring in most of the sections of the United States and in many foreign countries. It is quite rare; according to the statistics of the American Dermatological Association for 1921, there were only 21 cases of cutaneous blastomycosis in a total of 48,611 skin diseases.

Symptomatology—*Cutaneous Blastomycosis.*—The disorder usually attacks the exposed surfaces, the face, hands and arms, but any part of the body may be implicated. The primary lesion appears as a small reddish papule or papulopustule, which slowly increases in size and is soon capped with a crust. As it grows larger, it becomes raised above the surrounding skin and irregular papilliform elevations appear on the surface. The papillæ may be smooth, glistening and reddish in color, or dark and wart-like in appearance. Crust formation may be present if the secretion of pus is abundant, and small superficial ulcers may occasionally develop when a secondary infection with pus cocci has occurred. The patch is sharply defined from the surrounding skin and has an abruptly elevated dark red or purple edge which contains minute intradermal abscesses varying in size from microscopic ones to those as large as pinheads. These are quite characteristic of the disease and, when a portion of the border is squeezed between the fingers, minute droplets of pus will usually be forced out upon the surface. After a time reparative processes take place and more or less scar formation develops which may result, especially upon the face, in considerable disfigurement from contraction.

The original patch may persist alone for months or years, but usually, as a result of auto-inoculation, other lesions appear in the adjacent skin or on other portions of the body. Areas the size of the hand or much larger may result from the confluence of two or more lesions.

The disease is very chronic and may be characterized by periods of remission, but most of the patches, if untreated, show a slow continuous peripheral extension. Occasionally there may be a new invasion in a scarred surface which had apparently healed.

The subjective symptoms are mild. Pain is not often troublesome and the patches are not sensitive to pressure. The general health does not seem to be impaired and it is very rare for systemic blastomycosis to result from the cutaneous variety. The neighboring lymphatic glands are usually not affected, unless as a result of a secondary infection.

Systemic Blastomycosis.—In this form of the disease infection usually takes place through the lungs and the earliest symptoms are most frequently those of an acute respiratory infection. An obstinate coryza, pain in the chest, dyspnea, fever and cough with a purulent expectoration may mark the onset. In some cases, however, secondary involvement of the skin may be the first sign to attract the attention of the patient. As the disease progresses, the symptoms are those of a chronic infection. There is emaciation, weakness, acceleration of the pulse, and irregular fever with occasional chills and sweats. Signs of lung involvement with bloody and purulent expectoration may be observed. Extensive internal changes and destructive processes, however, may be present without corresponding external manifestations. Symptoms referable to involvement of special organs may supervene, such as pain, from affections of the bones, and paralysis from the localization of lesions in the brain and spinal cord.

Involvement of the skin usually occurs early in the course of the disease. Nodules, abscesses and ulcers are the lesions usually met with. The abscesses may form in the skin, subcutaneous tissues or muscles and vary greatly in size. They usually rupture on the surface with the formation of irregular ulcerations, or sinuses when they are very deeply located. Occasionally papillomatous vegetations, similar to those seen in cutaneous blastomycosis, may spring from the bases of the ulcerations.

The blood usually shows a leukocytosis. The fungus is found in the pus and sputum; it has also been recovered from the blood, urine and feces. Recovery rarely occurs.

Etiology and Pathology.—The disease is due to a budding fungus which was discovered in a cutaneous lesion by Gilchrist in 1894. There are perhaps several varieties and considerable difference of opinion exists as to the proper botanical classification.

The organisms can be easily demonstrated in pus squeezed from the edge of a verrucose patch on the skin, or from an abscess, by mixing a small amount with 10 per cent potassium hydroxid and after thirty minutes examining under the microscope with reduced light. They appear in variable number as yeastlike, round or oval cells with a granular protoplasm and a double-contoured refractile capsule. They vary in diameter from 5 to 15 microns, averaging about the size of a red blood-corpuscle. Budding forms are usually present. Growth in the tissue takes place only by budding, but there may be mycelial formation on artificial media. Lesions similar to those in man may be produced in animals by inoculation and the organism be recovered in pure culture.

In the cutaneous variety infection probably takes place through minute injuries to the skin; in the systemic form, in the majority of cases, through the lungs. Only very rarely does the disease become generalized when the primary infection is in the skin. Unhygienic surroundings, especially where there is much dampness, apparently predispose to infection. Stober was able to demonstrate organisms similar to blastomyces on moldy wood in the living quarters of patients affected with the systemic variety.

The pathological changes in the skin consist of a cellular infiltration in the cutis of plasma cells, lymphocytes, endothelioid and usually giant cells. The most characteristic changes are the miliary abscesses contained in the hypertrophied epidermis within which the organism can usually be recognized.

In the systemic variety the gross pathological changes consist of granulomatous nodules or ulcers scattered through the various organs and tissues. The wide distribution of the infection and the multiplicity of foci is a characteristic feature.

According to the statistics of Wade and Bell, the lungs are implicated in 96 per cent of the cases, the skin in 89 per cent, the bones in 59 per cent and other organs in a decreasing proportion.

The changes in general resemble those of tuberculosis with the exception that suppuration is more marked. A generalization of miliary nodules may simulate miliary tuberculosis or there may be changes in the spine giving rise to the picture of Pott's disease.

Microscopically, the nodules consist usually of a central area of necrosis with giant cells. Outside of this there is a zone of granulation tissue surrounded by lymphocytes, plasma cells and leukocytes. Numerous blastomycetes are present in the necrotic tissue and in the giant cells. In some lesions, however, there is no definite order of arrangement and the different elements are mixed together promiscuously.

Although the process, when not limited to the skin, is usually found widely distributed throughout the body, a few cases have been reported in which it was apparently localized in other organs or tissues of the body, epididymis, spine, tibia and larynx.

Treatment of Cutaneous Blastomycosis.—In this form of the disease the prognosis is good. Potassium iodid, first recommended by Bevan, has proved more valuable than any other drug. It should be administered in doses beginning with 10 gr. three times a day and increasing as rapidly as possible up to 50 or 60 gr. a day. In some cases, however, it has been necessary to give 300 or 400 gr. per day before its beneficial results were noticed. While complete cure may occasionally result from this treatment alone, some of the diseased tissue usually remains and relapses are liable to occur unless local destructive methods are used.

Bevan has noted favorable results from the administration of copper sulphate in ¼ to ½-gr. doses three times a day. He combines this with a 1 per cent solution of the same drug used as a local wash.

Peterson reports rapid healing of the lesions in 3 cases of the disease showing ulcerative lesions in the skin following the injection of 1 to 4 doses of arsphenamin. Two of these cases had been diagnosed as syphilis and the patients had been getting potassium iodid and mercury.

Vaccine therapy has been tried in a few instances with encouraging results. Pels, in Gilchrist's laboratory, treated 3 cases with a filtrate from a three-months-old culture of blastomycetes. The filtrate was given every two or three days, beginning with 1 c.c. and increasing to 10 c.c., after which a general reaction was noted. A marked improvement was observed in the lesions, but treatment was not continued to a definite conclusion, as the filtrate became exhausted.

Stober also noted improvement in 1 case from the injection of the filtrate and a suspension of the organisms.

Cole reports a favorable reaction on the course of the disease after injections of foreign protein such as typhoid bacilli. He has also found that the response to other methods of treatment are better when preceded by these injections.

Various procedures for the *local destruction of the lesions* have been used. The thoroughness with which it is carried out is of more importance than the selection of any particular method. If the diseased area is small and favorably situated, excision may be possible. A thorough curettage and cauterization of the base of the lesion would answer the same purpose. In most cases, however, the patches are too large or are so situated that surgical measures cannot be successfully employed. In such cases X-ray therapy has perhaps proved the most valuable.

Most of the observations published concerning this form of therapy preceded the modern era of X-ray therapeutics and accurate measurements were not possible, but the applications were made in a way similar to what is now known as the fractional method, that is, in small doses frequently repeated. At the present time, however, the massive dose method has proved to be of the greatest value in most conditions when a destructive effect is desired.

MacKee reports that he has treated several cases of the disease with both methods and has had a relapse in only one instance. In most of them the lesions disappeared as a result of one or two intensive treatments or of from six to twelve fractional applications. If the massive dose method is selected, H1 to H2 S.D.[1] units, unfiltered, should be given at one time. The size of the dose should depend upon the depth of the pathological tissue and its location. It may be repeated in from four to six weeks' time if necessary. If the fractional method is used, H¼ units may be given at weekly intervals until the lesions are cured or the lack of response makes discontinuance of the treatments advisable.

Radium would probably be of equal value with X-rays and in some locations could be used to better advantage.

Local hygienic measures should be combined with any of the foregoing procedures. Where there is much secretion, mild antiseptics should be used to keep the affected areas clean.

Treatment of Systemic Variety.—In this form of the disease the prognosis is grave, 90 per cent of the cases reported having ended fatally. Potassium iodid should be given and general measures adopted for stimulating the patient's powers of resistance, as is done in any chronic infection.

Symptomatic treatment may be necessary for the relief of cough, pain and other discomforts. General surgical measures are indicated in taking care of the ulcers and abscesses which develop in the skin or underlying tissues. The destructive methods used in the treatment of the cutaneous variety are of little value when the disease becomes generalized. The ulcers should be dressed with antiseptics, the abscesses opened and evacuated of pus and irrigated with 1 per cent copper sulphate or a weak iodin solution.

If the disease is not too far advanced it is possible for vaccine therapy to be of value. Stober treated two cases of systemic blastomycosis in this manner besides the one of the cutaneous variety referred to above. In one instance in which the disease was far advanced the patient was not benefited, but in the other a remarkable improvement was brought about.

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CHAPTER XXVII

COCCIDIOIDAL GRANULOMA

Herbert C. Moffitt

Since the papers of Ophüls in 1900 and 1905, coccidioidal granuloma has been endowed with features distinctive enough to warrant separation from other forms of oïdiomycosis. Although the parasite has never been found except in the varied lesions of the disease as observed in man, it grows readily on artificial media and may be transmitted to guinea pigs, rabbits and other small animals by inoculation of pus or sputum or of old spore-bearing cultures. As found in pus, sputum or various tissues of the body the parasites appear as spherical bodies averaging about 30 microns in diameter with highly refractile double-contoured capsules. They stain poorly and should be looked for in fresh specimens of pus, sputum or tissue suspensions. In the host, reproduction occurs by endosporulation, the protoplasm dividing until fifty or a hundred or more spores are packed tightly within the capsule. Increase by true budding, a characteristic of the closely related organism of blastomycosis, has never been observed. On culture media the parasite grows as a thick white mold with short hyphæ which later develop terminal spores. In hanging drop preparations Ophüls observed the development of hyphæ from the spherical bodies by a process of outgrowth through the capsule. His experiments would indicate that infection of animals does not occur from fresh growths on artificial media with the mycelium alone, but only from old spore-bearing cultures. Intraperitoneal inoculation of material into male guinea pigs or rabbits is followed by hard swelling of the testes with later suppuration and sinus formation—a most useful diagnostic procedure.

Pathology.—Pathologically and clinically the disease most closely resembles tuberculosis. In acute generalized forms there may be miliary tubercles in all organs of the body. In the lungs, lymph glands and abdominal viscera of more slowly progressing cases there may be extensive caseation with little tendency to suppuration. As in tuberculosis the adrenals are frequently involved. Suppuration is the rule in lesions of the subcutaneous tissues, bones and joints; both suppurative periostitis and osteomyelitis occur. Primary lesions of the skin are frequent. Painless hard nodules gradually increase in size, slowly ulcerate, discharge considerable amounts of pus from a granulating base, and are covered by thick dry crusts. Individual lesions may heal under local treatment, but dissemination eventually occurs by way of lymph glands or blood-stream and generalization of the infection results. In Posada's case infection remained limited to the skin for seven years, in one of Rixford's cases for nine years. Meningeal localization is important to remember clinically. In a boy of seven recently in the University of California Hospital internal hydrocephalus followed basilar meningitis of fourteen months' duration. Typical spherical bodies were found in the thickened meninges and in a small primary lung focus.

The course of the disease may be rapidly downward to a fatal issue within a few weeks with the clinical picture of typhoid, sepsis or generalized tuberculosis. A moderate leukocytosis is generally present. Enlargement of the spleen has been noted. Localization of more chronic lesions in skin and subcutaneous tissues may lead to confusion with glanders, syphilis, tuberculosis or blastomycosis. Localization in joints has led to resection for tuberculosis. Chronic pulmonary forms are usually mistaken for tuberculosis; sputum is mucopurulent and hemoptyses are frequent; the clinical and X-ray signs are not distinctive but careful examination of the fresh sputum will help in diagnosis. In a case of Chipman with parasites found microscopically in the skin lesions, tubercle bacilli were present in the sputum; and in a case in my service some years ago with multiple subcutaneous bone and pulmonary lesions, death occurred from cancer of the lung. Even with unusual course, or localization, or complications, diagnosis can nearly always be made if it be remembered that the disease is practically confined to individuals who at some time have lived in the San Joaquin Valley in California. The characteristic spherical bodies with double capsule occur in large numbers in pus, sputum and skin lesions. Cultures grow readily and intraperitoneal inoculation of pus or tissue suspensions into male guinea pigs or rabbits gives typical testicular enlargement and suppuration.

Prognosis.—The prognosis of the disease is extremely bad. As far as is known only 4 cases escaped general infection. The chronicity of certain skin manifestations has been noted above. One patient of S. J. Gardner remained well after resection of the elbow and another after amputation of the leg for ankle joint involvement.

Treatment.—Radical treatment is advisable for lesions localized in the extremities. X-ray treatment of skin nodules and ulcers has occasionally seemed beneficial. It should be tried also in bone, joint and lung involvements. Incision, free drainage and irrigation with Dakin's solution is the best treatment of subcutaneous abscesses. Various dyes have been used locally in abscesses and joint and bone disease without specific effect.

Iodin and iodids, of great value in actinomycosis and blastomycosis, have been useless in coccidioidal granuloma. Arsphenamin, cacodylates, colloidal copper, and copper sulphate have been tried by the writer without result. In 1 case, dying later of cancer of the lung, intravenous injections of antimony potassium tartrate seemed of subjective and even objective benefit. In view of its action in bilharziosis, leishmaniasis and peruvian Granuloma, the drug should be given further trial. Initial intravenous injection of 5 c.c. of a 1 per cent solution of tartar emetic may safely be given to adults, and the dose quickly increased to 10 or even 20 c.c. Large doses should be given only two or three times a week.

Vaccines have been prepared and used in treatment by J. V. Cooke and Karl Meyer. Pus from skin, joint or bone lesions is collected in large amount—a liter or more—treated with antiformin and the parasites centrifugalized out, washed and sterilized in an autoclave. Cultures are also prepared on Sabouraud's Agar for three or four weeks, the growth scraped off and autoclaved long enough to kill all spores. Mixtures of these two preparations are made in about equal proportions. There is no definite method of standardization and dosage has been wholly empirical. No positive results were obtained in 2 cases personally observed.

CHAPTER XXVIII

FUNGUS INFECTION

Charles P. Emerson

GENERAL CONSIDERATIONS

Although the first two of all the pathogenic microörganisms to be discovered (the organisms of favus and of thrush) were fungi, yet the importance in human pathology of yeasts and molds has until recent years been little appreciated. Evidently it was necessary first that bacteriology should reach considerable development, since the mechanism of infection by the less pathogenic fungi would seem to be different and their relation to disease more difficult to prove than in the case of the bacteria. The well-known bacteria are easier to grow; they have a simpler and more constant morphology; they are not as easily rendered unrecognizable by our technic; and finally, in their infections we can demonstrate and experiment with the specific toxins which they produce and also with a variety of specific antitoxins and other protective bodies which they stimulate the infected individuals to produce, the demonstration of either of which is almost as satisfactory as is that of the organism itself. But the fungi seldom, if ever, affect the organism as a whole. It is claimed that some of them produce toxins and, what is more important, since therapy is our subject, that by animal experiment we can prove that some of them stimulate the production by the animal of demonstrable specific and nonspecific antibodies. But in human pathology neither is as yet definite enough to be of value either in diagnosis or in therapy.

For the most part the fungi merely destroy the tissue locally where they grow. These local ravages may be extreme, and yet the patient does not lose weight or strength and feels no malaise. These fungi certainly can penetrate tissues and that they do destroy it is shown by the large cavities which they produce in the subcutaneous tissue, liver and lung; but according to our present knowledge, the mechanism of this tissue destruction, when not due to secondary or associated bacteria, would seem to be more by means of simple proteolytic ferments than by the action of specific toxins capable of arousing active protective chemical defense. Finally, their mycelial threads would seem to penetrate a solid tissue more by direct extension along the lymph channels and through tissue spaces than by actual penetration or destruction of the cells and the most of the injury they produce is mechanical rather than chemical. How these organisms get their first foothold in the human body is not clear, but infection by them would at least seem difficult; once started, however, their growth often is most persistent, and since they stimulate the production of little or no immunity, their infection evidently is not self-limiting and therefore their therapy is most difficult.

To understand the human mycoses it was also necessary to wait until our too positive ideas concerning the infectious diseases had been shown to be inadequate and we had begun to realize that the mechanism producing some at least of the specific diseases, meaning by this term those symptom complexes which received their names long before their cause had been discovered, is not as simple as has been supposed. Some at least of these specific diseases are not "pure infections"; at least the clinical picture of a "pure infection" by certain pathogenic organisms is not identical with the diseases of which these particular pathogenic organisms are supposed to be the specific germs. Many diseases would seem, rather, to be due to two or more pathogenic organisms, and the results they produce is not the sum total of the activities of each, had it been alone. The problem is not one of "secondary infection" as that term usually is understood; that is, an infection which like a weed accidentally infects susceptible soil, although it might include that; but the problem is rather one of definite "team play" of organisms, one of which so affects the tissue soil that another wave infection can follow, each producing results which depend in part at least on the previous preparation of the soil by the preceding organism. It would seem to be through some such relationship to other pathogenic or non-pathogenic microörganisms that fungi best express their pathogenic properties. Only in this way can we explain the remarkable pleomorphism which these organisms show when studied in connection with the various lesions which they produce; the variety of lesions of very different severity which the same form produces; the practically constant association of fungi and certain bacterial forms; and finally the impossibility of producing a characteristic lesion, or any lesion at all, with a pure culture of some fungi although this lesion is easily produced if the infected tissue or a secretion containing the fungus is used. Until we understand better what these relationships are, our therapy of fungus infection will continue to be unsatisfactory.

CLASSIFICATION OF FUNGI

A satisfactory discussion of fungus diseases presupposes a satisfactory discussion of the classification of these plants. To identify a fungus it is not enough to study the organism as we find it in the human tissues or in secretions. One must study it also in cultures and in the tissues of experimentally infected animals; and even then their identification is most difficult. The cultural studies are most unsatisfactory since these organisms are very sensitive to variations in media. Even Sabouraud's media (maltose 40 gm., peptone 10 gm., distilled water 1,000 c.c., agar 18 gm.), simple though it seems, must, it is said, be made from the French ingredients if we are to get results comparable with those of Sabouraud. Four per cent glucose agar or glucose blood agar are among the best media. Often one succeeds by spreading the sputum, for example, on a piece of bread soaked in milk and sterilized in a Petri dish, but this is not always satisfactory. To examine the fungi in infected tissues is also very difficult since the mycelial threads, though abundant, cannot be recognized in tissues stained in the usual manner. The molds in the fresh specimen may be stained by a saturated watery solution of safranin or, better still, of thionin.

Formerly we divided fungi into yeasts and molds, and taught that yeasts multiplied by budding and molds by ascus formation. This is quite incorrect since under certain conditions many "molds" can be made to reproduce by budding and many "yeasts" if properly grown will produce ascospores. To the botanist the ascus spore formation is the starting point in their classification; but this may be seen only under very artificial conditions or not at all under the conditions we now create. And yet this is the best we can do now, and unsatisfactory though it is we shall proceed to follow it.

The fungi pathogenic to man all belong to one of the two great primary divisions of these plants, the Eumycetes, whose vegetative body is generally filamentous. (The members of the other primary division, the Myxomycetes, have as vegetative body a multinucleate naked plasmodium. Among these are no parasites of man).

Of the four subdivisions (classes) of Eumycetes (we follow Castellani) the pathogenic fungi belong in three: ***CLASS I, FUNGI IMPERFECTI*** (mycelium septate; ascospores not as yet demonstrated); ***CLASS II, ASCOMYCETES*** (mycelium, when present, septate; ascospores demonstrated); and ***CLASS IV, PHYCOMYCETES*** (whose mycelium is non-septate in the vegetative stage). In ***CLASS III, BASIDIOMYCETES*** (mushrooms and rusts) there are no members pathogenic to man.

The class ***FUNGI IMPERFECTI*** is most important of all to physicians, because of the many important parasites which it contains. The student should understand, however, that in the case of many of these fungi the adjective "imperfect" is quite as descriptive of our knowledge as it is of the life history of the parasite. Some of them may actually have simpler life histories than the ascomycetes, that is, may be "imperfect"; but many are placed in this class merely because no botanist has as yet succeeded in demonstrating that they do produce ascus spores. Should one succeed, the classification of that organism would at once be changed.

The ***IMPERFECT FUNGI*** are subdivided into two groups: (*a*) **Deuteromycetes,** with accessory fructifications present, a group which has no medical interest; and (*b*) **Hyphales** or **Hyphomycetes,** with (according to our present knowledge) accessory fructification absent. This group contains many important pathogenic fungi.

The **Hyphales** are classified in four orders: MICROSIPHONALES, THALLOSPORALES, HEMISPORALES, and CONIDIOSPORALES.

MICROSIPHONALES

MICROSIPHONALES (their hyphæ bacilliform), of which there are two families: the MYCOBACTERIACEÆ and the NOCARDIACEÆ.

a. The MYCOBACTERIACEÆ produce, so far as we know, no mycelium and usually are classified with the bacteria. Four genera of this family are of medical interest: *MYCOBACTERIUM, LEPTOTHRIX, CLADOTHRIX* and *VIBRIOTHRIX.*

The members of the genus *MYCOBACTERIUM* when met with in clinical examinations and not further studied are usually carelessly referred to as "diphtheroid bacilli" or "diphtheroids" (although it must not be understood that all, or even many, of this ubiquitous group of organisms which morphologically resemble Bacillus diphtheriæ belong to the genus Mycobacterium). These "diphtheroids" as a group, for which the name Corynebacterium has been suggested, are Gram-positive, non-motile organisms which do not produce spores and which often contain metachromatic granules. They are easily found in the mucus of the nose, throat, in the skin and lymph glands and are frequent contaminations of blood cultures if carelessly made. It was one of these (Corynebacterium hodgkini) which Bunting and Yates reported as the cause of Hodgkin's disease.

Belonging to the genus *MYCOBACTERIUM* is the group *Anaëromyces,* which is of importance in human pathology. This differs from the group Corynebacterium in that its branching is much more marked and that it is strictly anaërobic. It differs also from the genus Nocardia in that its mycelium is much less developed, its growth is not dry but is moist, is crinkled, and in that in the lesions it causes it never gives rise to actinomitic granules.

Broncho-anaëromycosis.—Castellini, Douglas and Thomson reported a form of hemorrhagic bronchitis found in Europe as well as Asia, due to Anaëromyces bronchitica, a much branching, Gram-positive, not acid-fast, non-motile, obligate anaërobic diphtheroid bacillus which measured from 3 to 5 microns long and 0.3 micron in breadth. Anaëromyces is grown occasionally from bronchial cases in which monilia and other fungi and also Bacillus tuberculosis, are present.

Two groups of cases of Anaëromyces bronchitica have been separated: (1) the hemorrhagic type, and (2) the mucopurulent type. Cases of the hemorrhagic type closely resemble pulmonary tuberculosis in that there may be an intermittent or remittent fever, anemia, loss of weight, and bloody sputum which at times has a very characteristic bright, brick-red color. The physical examination of the chest may be at times almost negative and at other times may on percussion show patches of impaired resonance where crepitant râles are heard.

Cases of the mucopurulent type resemble ordinary subacute or chronic bronchitis. There may be slight fever and yet the general condition of the patient for a long time is not affected. The sputum is mucopurulent or at times frankly purulent. These cases after a variable period of time may become hemorrhagic.

There is a dispute whether or not these fungi actually caused the bronchitis of the patients in whose sputum they were found. In favor of this is the point that they rapidly decreased in number and finally disappeared with the gradual improvement of the bronchial condition and also that these cases improve under treatment directed against infection by this fungus.

The organisms of the genus *LEPTOTHRIX* are simple, unbranched threads. They are often found in the lesions of cases of stomatitis and pharyngitis, but whether they cause, or help cause, these lesions is a disputed point.

CLADOTHRIX is a threadlike form which seems to, although it does not, branch; that is, after the end of the thread has broken off as an independent cell the parent thread will continue to grow past this new one which now because of its position will resemble a branch.

b. The second family of the order MICROSIPHONALES, the Nocardiaceæ, includes those organisms of this order which form a definite mycelium. Of this family there are two genera: *NOCARDIA* and *COHNISTREPTOTHRIX*.

The organisms of the genus *NOCARDIA* grow in branching filaments made up of bacterialike units, are aërobic, easily cultivated, produce arthrospores and, what is more important, do not produce the granules or "drusen" characteristic of actinomycosis. It adds to our confusion that some of these bear the names Streptothrix, Cladothrix, Actinomycosis, and still others Oöspora and Discomyces. This genus evidently is of great importance not only since it includes organisms important in human pathology but also because they are a source of considerable error in diagnosis.

Cladothrix asteroides, the type form (so-called because of the star shape of the young colonies growing on agar) also called Streptothrix eppingeri and Actinomycosis asteroides, has been cultivated from the bronchial lymph glands, the pus of brain abscesses, pleural pus, meningeal pus, and from a case of Madura foot. It is easily grown on culture media. Most of the organisms isolated are pathogenic for laboratory animals. In smears of pus it is found as long, tortuous, branching, Gram-positive, and acid-fast filaments. It differs from the genus Cohnistreptothrix in that it forms in lesions no actinomitic granules, is readily cultivated, forms, as a rule, no clubs, and is very pathogenic to laboratory animals.

This organism, especially the fragments of the older threads, is definitely acid-fast and, when only a few fragments and no long threads are seen in smears of sputum stained for Bacillus tuberculosis, may easily be mistaken for this organism. It has been roughly estimated that, of all the positive reports of the presence of Bacillus tuberculosis in the sputum made in laboratories where many sputa are examined by routine methods, one in ten will be an error because of these and similar acid-fast fungi whose filaments when old break up into bacilliform fragments. Realizing this possibility the laboratory workers usually warn the physicians that all positive reports should be confirmed; but this is not always done. From the study of 26 reported cases of nocardiosis including 1 of their own, Henrici and Gardner suggested that there were three varieties of this parasite, which differed in pathogenicity to laboratory animals, in their reaction to oxygen, in their growth on different culture media and in their acid-fast qualities.

In the cases reported the portal of entry would seem to be the bronchial tree, and the primary infection was the bronchial lymph glands. By metastasis later these fungi might cause bronchopneumonia and subsequently pulmonary abscesses, abscesses of the pleura, and especially abscess of the brain. By hematogenous distribution they produce a miliary pseudotuberculosis. Macfie and Ingram isolated from the blood of a patient who died of an obscure complaint a fungus of this genus but different from others described and for which they suggested the name Nocardia cruoris. Gray reported a case of nocardiosis cutis which resembled sporotrichosis.

The cases reported have the widest distribution. No relation to grain can be made out. No systemic treatment was reported in connection with any of the above cases.

The second genus of the Nocardiaceæ, *COHNISTREPTOTHRIX,* does not produce arthrospores, does not grow well on ordinary culture media, practically not at all at room temperature, and grows best anaërobically. It is but little pathogenic to laboratory animals.

Belonging to this genus is the group *Actinomyces,* characterized by the formation in lesions of characteristic granules or drusen. These microscopically show the stellate arrangement of the mycelial threads with club-shaped ends which form the periphery of these actinomitic bodies. The most interesting subgroup of this group is Streptothrix actinomycosis and of this the most interesting member is Streptothrix israeli (Cohnistreptothrix israeli), the cause of human actinomycosis (see Chapter XXIII, page 359).

Streptothrix Freeri.—In the actinomycosis group belong at least some of the organisms which cause mycetoma or Madura foot (see page 387). In the discharge from the fistulæ present in these cases one sees black, white, yellow (ochroid the commonest variety) or red granules. The black granules (Wright) are seen under the microscope to have a dark, almost opaque center surrounded by a border made up of a mass of thickly matted, very long, septate mycelial threads which are thick, often swollen and much branched. No spores are seen. This organism is easily cultivated. Animal inoculations are unsuccessful. The more common granules, the yellow or ochroid granules, contain a streptothrix described under the name Streptothrix freeri.

MYCETOMA, FUNGUS FOOT, or MADURA FOOT, an endemic disease of India, but sporadic in temperate climates, is a chronic infection of the foot, but also, although rarely, of the hand, knee or elbow, due to several species of streptothrix but especially Streptothrix freeri. This streptothrix gains access through some slight wound or break in the skin and slowly, during the next few days or weeks, transforms the subcutaneous tissue into an inflamed and swollen mass in which firm, rounded nodules (infectious granulomata) develop which give the affected area a reddened or purplish, knobby appearance, not unlike that seen in actinomycosis. Later these nodules break down and the tissues of the foot become transformed into a swollen mass, made spongelike by the many abscesses which discharge, through many (from eight or ten to a half hundred or more) long, narrow, tortuous sinuses, an oily, seropurulent fluid containing many yellowish, reddish or brownish fish-roelike granules called "druses" or "grains." By this time the part has become so enlarged, swollen, and misshapen that it has almost entirely lost its original outline, and, as a result of disuse, the affected limb later becomes shrunken and wasted.

Several other organisms may cause this disease; for example, Cladothrix asteroides (see page 385).

The subjective symptoms of which these patients complain are remarkably trivial. The internal organs do not become involved. Lymph-node involvement occurs only as a result of secondary pyogenic infection. When once the nodules have broken down there is no evidence of spontaneous healing. The malady may extend over a period of even decades and seldom, if ever, directly causes death.

Treatment.—This infection is very resistant to treatment. Internally, iodin in large doses is the most reliable remedy. Locally, curettage, the X-rays and caustics may be tried. Excision of the affected part, however, usually offers the only hope of permanent relief.

THALLOSPORALES

The second order of the **Hyphales**, the THALLOSPORALES, reproduce by thallospores (that is, by sporelike bodies which are portions of the vegetative body, the thallus, secondarily adapted for reproduction). One suborder of this order, the BLASTOSPORINEÆ, which reproduce by blastospores (round or oval thallospores produced by simple budding, a method of reproduction formerly supposed to be characteristic of the yeasts), contains five families: (1) the CRYPTOCOCCACEÆ, with hyphæ hardly different from conidia, and both yeastlike, and the conidia not arranged in chains: (2) the OÖSPORACEÆ, with long hyphæ and spores typically in chains: (3) the ENANTIOTHAMMACEÆ, with conidia arranged verticillate around the septa of the mycelial hyphæ; (4) the HAPLOGRAPHICEÆ, whose conidia (if the organism is living as a parasite) form in grapelike masses; and (5) the CLADOSPORIACEÆ, with conidia solitary or in chains.

With the CRYPTOCOCCACEÆ are usually placed the Blastomycetes. The classification of these very important pathogenic organisms (the Blastomycetes) is most unsatisfactory. Usually described as "yeasts" or yeastlike forms, because their most conspicuous method of reproduction was by budding, they formerly were supposed to be simpler even than the imperfect fungi. More recently, however, the ordinary yeasts have been promoted as the family Saccharomycetaceæ to the Class Ascomycetes.

Associated with this organism is another variety of this same genus, Coccidioides immitis (Oidium coccidioides) the cause of Coccidiosis (Coccidioidal Granuloma: California disease; San Joaquin Valley Disease; Mycoderma immite) (see Chapter XXVII, page 378).

The second genus of the OÖSPORACEÆ, *MONILIA,* is a rather ill-defined group of fungi which, in the infected tissues presents free budding forms (blastospores) and also mycelial threads of rather large size, in masses, made up of short irregular units, which become easily detached, and others which are long and branched, and which often present arthrospores. Grown on solid culture media, this group grows as round or oval budding yeastlike cells with either no, or only a few, short mycelial threads.

Bronchomoniliasis.—This form of bronchitis found in the temperate as well as tropical and subtropical countries is due to various species of Monilia, especially Monilia tropicalis, Monilia krusei, Monilia pinoyi and Monilia metalondinensis.

Clinically mild, intermediate and severe types of this infection are met with. In the mild cases the general condition of the patient is good, there is no fever, and the expectoration is mucopurulent, often scanty, and does not contain blood. The physical examination of the chest is negative, or reveals only a few râles. In these cases the infection may last for several weeks or months and then may recover spontaneously, or may develop into the severer type which resembles phthisis. In these severer cases there is hectic fever, emaciation and bloody expectoration. The physical examination of the chest may on percussion show patches of bronchopneumonia over which fine crepitations and pleural friction rub, etc., are heard. This type may end fatally.

Diagnosis.—The diagnosis of this condition is based on the absence in the sputum of Bacillus tuberculosis and the presence of monilias. In all such cases it is essential that the sputum should be collected in sterile receptacles after the patient has gargled his throat thoroughly with warm sterile water. Sometimes one finds monilia in the fresh sputum as spore-like, roundish or oval cells with a double contour, or occasionally as fragments of mycelial threads. In other cases the monilia is found only by cultural methods. In no case should a definite diagnosis or bronchomoniliasis be made before the organism has been demonstrated in cultures. A small amount of sputum is smeared on several tubes of glucose or maltose agar, and these are incubated at a temperature of 22° to 25° C. In two or three days white, rather large, roundish monilia colonies will appear. To determine the species of the monilia the organism isolated should be studied with reference to its growth in milk, its development on gelatine and on blood serum, and its reaction to certain carbohydrates: glucose, levulose, maltose, galactose, saccharose, inulin and dextrin.

That many of the cases of bronchomoniliasis are secondary, developing in cases of tuberculosis and other chronic pulmonary conditions, is admitted. The diagnosis of primary bronchomoniliasis is, however, difficult since monilia fungi are frequently very abundant in the air in tropical countries and so quickly contaminate samples of sputum; they are also not rare as saprophytes in the mouth; and, lastly, non-pathogenic monilia fungi may be present in the bronchial mucus. A definite diagnosis of primary bronchomoniliasis, therefore, is justified only when tubercle bacilli are absent, when the bronchial expectoration has been collected and preserved with every possible precaution; when it contains a monilia in fair numbers; and if their number decreases rapidly as the condition of the patient improves. In other cases, however, the monilia infection of the bronchi complicates pulmonary tuberculosis.

Treatment.—The treatment of this form of bronchitis is potassium iodid with which the glycerophosphates and balsams may be associated. Castellani admits, however, that in some cases potassium iodid has practically no beneficial action. Vaccines have, it is claimed, occasionally been useful.

The genus *MONILIA* contains an important group of fungi, the type form of which is Oïdium albicans (Monilia albicans) the cause of thrush. For a critical discussion of this organism, as belonging to the genus

Oïdium, see Fineman. Castellani, on the other hand, states that Oïdium albicans belongs to genus Monilia.

This is the most common parasite of the thrush of children, especially that of weak babies, but is found also in the thrush of older children and of adults weakened by old age or disease. Oïdium albicans is seen in two varieties: the large-spored (the more common) and the small-spored varieties. It is found in the sputum in two forms: yeast forms, that is, oval cells, from 5 to 6 microns long and 4 microns wide, which bud; and doubly contoured mycelial threads of all sizes and lengths with thick cross walls which develop, true endogenous spores and which contain also droplets, granules, and vacuoles. It differs from the Endomyces albicans chiefly in that no asci have as yet been demonstrated. In cultures it multiplies also by budding and develops a mycelium with conspicuous chains of conidia growing from the sides and ends of the mycelial threads. Mycelium formation is favored by anaërobic conditions, by an alkaline medium, and by scarcity of carbohydrate in the medium; budding, on the other hand, is favored by aërobic conditions, by a medium rich in sugar, and by an acid medium.

Many fungi may be found in the membrane of thrush. Castellani tabulates at least nineteen. Most of them would seem to be imperfect fungi and are best illustrated by the above organism. But fungi of other classes also are found, for example, Endomyces albicans and Aspergillus fumigatus.

Thrush.—Thrush, or parasitic stomatitis, is an infection of the mucous membrane of the mouth by one or more of the group of so-called thrush organisms and is characterized by the formation there of a membrane which is pearly white in color (that of diphtheria is yellowish or grayish white) and so loosely attached to the mucosa that the least touch will loosen large fragments, leaving the underlying mucosa red and slightly bleeding (the membrane of diphtheria cannot thus easily be removed and where removed leaves a raw bleeding surface). In this membrane the mycelial threads and spores of the yeasts are easily demonstrated. The most common site of this membrane is on the soft palate and tonsils, the inside of the cheeks and the posterior pharyngeal wall; but it may cover the entire interior of the mouth. It may also spread to the nose or esophagus, stomach and bowel, in which case it may cause a diarrhea. It may appear in the vagina and on the nipples of nursing women. Finally, metastases of the infection causing abscess of the brain, lungs and kidneys have been reported.

While the thrush of children and healthy adults may be a trivial condition, yet for cachectic adults weakened from chronic diseases, such as tuberculosis, cancer, typhoid fever, diabetes, etc., this infection is by no means negligible.

Treatment.—Thrush may be prevented by feeding the children pasteurized milk and by cleaning thoroughly all the bottles, nipples, etc., used. The membrane if present may easily be removed by wiping the infected areas with a piece of soft gauze soaked in boric acid or sodium bicarbonate solution and then spraying the mucosa with these solutions or with 1:4,000 mercuric bichlorid, 1:25 sodium hyposulphite, weak borax, or potassium permanganate solution.

The fungi of the genus *OÏDIUM* are similar to monilia but mycelial threads are very abundant both in lesions and cultures and budding yeast-like forms are rare.

Castellani found three species of this genus: Oïdium matalense, Oïdium asteroides, and Oïdium rotemdatum in the membrane of thrush of the tropics, in cases of tonsillitis and bronchitis, and in the stools in enteritis.

The second suborder of the THALLOSPORALES, the ARTHROSPORINEÆ, reproduce by arthrospores. (Thallospores are spores formed simply by the segmentation and disarticulation of a mycelial thread. These are square in shape first but later are round). This suborder contains the very important family of the Trichophytonaceæ, among which are some very important parasites of hair. Among the genera of this family are the well-known *TRICHOPHYTON, MICROSPORIUM* and *TRICHOSPORIUM* and *ACHORION.* (The student should note that many authorities group these parasites as Ascomycetes of the family Gynnoascaceæ.)

Favus.—*Achorion,* the type species of which for man is Achorion schönleinii, the cause of favus, forms in the scalp large masses, called scutula, which are composed of the hyphæ of this fungus mingled with masses of rounded sporelike bodies (conidia spores) of various sizes crowded together at the center without definite arrangement. This fungus is characterized by the great variation of size of its filaments which also are crooked and of irregular contour. Some, indeed, are made up of chains of oval cells. Pear-shaped conidia are scattered along the sides of the delicate filaments but never occur in clusters; numerous chlamydospores (encysted arthrospores of large size) are present, some terminal, but more intercalary. The diagnosis is made by examining a scutulum in NaOH under the microscope and looking for the typical fungus (see Vol. VI, Chap. XXIX).

Ringworm.—*Microsporon* (type species, Microsporon audouini) the small-spored fungus of ringworm of the scalp and skin of children, appears in the epidermis as curved, branching hyphæ made up of long elements. Some of these fibers penetrate and grow along the medulla of the hairs, from which point they send out through the cortex lateral branches which produce a sheath which completely covers the stumps of the diseased hairs, composed of small round spores, 2 microns in diameter. This fungus is easily cultivated.

Trichophyton, the cause of ring-worm of the skin, hair and nails of adults, grows beneath the stratum corneum of the skin in the uppermost layers of the epidermis as long delicate threads, often tortuous and curved, but rarely branched. These form a mycelium, the threads of which produce a few large roundish or oval conidia arranged usually in chains. They form no scutulous masses. They penetrate into the hair shafts which they make brittle. To demonstrate this mold, the suspected scales, hairs and crusts are cleared in NaOH or KOH and examined microscopically. Several specimens should be examined before the search is abandoned.

Trichophyton differs from microsporon in that the threads which penetrate the hairs segment into chains of short mycelial elements which suggest (but are not) chains of spores. Sabouraud recognizes three primary divisions of this group: Trichophyton endothrix, found only within the medulla of the hair; Trichophyton neo-endothrix, similar to the former but which does develop a few filaments on the surface of some of the hairs; and Trichophyton ectothrix, which both invades the hair and proliferates actively on its surface.

According to other classifications one merely separates the large and the small-spored varieties.

Genus *EPIDERMOPHYTON,* type species, Trichophyton cruris (Epidermophyton cruris, Epidermophyton inguinale), one of the causes of eczema marginatum, grows in the epidermis as long interlacing filaments made up of oblong cells with double contour. It grows readily on cultures, where it forms no conidia, but instead produces innumerable blunt, club-shaped spores, borne on aërial hyphæ, which have smooth walls and which are divided into chambers by transverse parallel septa (fuseaux). Epidermophyton perneti and Epidermophyton rubrum (characterized by its deep red pigmentation when grown on Sabouraud's agar; that of Epidermophyton perneti is pale pink) also may cause this condition.

Tinea Versicolor.—Microsporon furfur, the cause of Tinea versicolor, is found abundantly in the horny epidermis as unbranched, septate filaments, 3 to 4 microns wide, with very irregular contour, which by interlacing form a meshwork enclosing masses of sporelike bodies which in form suggest bunches of grapes. If these are spores they are the largest seen of all the pathogenic fungi of the skin. The organism has not as yet been cultivated (see Vol. VI, Chap. XXIX).

Microsporon minutissimum (Sporothrix minutissimum, Nocardia minutissimum), the cause of erythrasma, looks like Microsporon furfur except that its fine twisted unbranched threads are much more delicate and easily break up into bacilluslike forms. Its minute spores lie in loose heaps.

Erythrasma.—Erythrasma (Baerensprung's disease) is a disease of those areas of the skin where two main surfaces oppose each other, therefore of the axillæ and groin. It is characterized especially by the presence of round, scaly, hyperemic patches due to a superficial invasion of the skin by Microsporon minutissimum. These patches have a pronounced tendency to become confluent, giving rise to areas as large or larger than a silver dollar.

The diagnosis can be made by examining the scraping microscopically.

Erythrasma is a persistent condition with a marked tendency to recurrence. The treatment is the same as that for tinea versicolor.

Monilia psilosis (Monilia enterica) has been described as the cause of sprue but more probably is merely the cause of some of the intestinal features (for example, the diarrhea) of this disease.

Monilia psilosis is a large, round, yeastlike organism, with very clearly defined contour, from 4 to 7 microns in diameter, with a granular and usually vacuolated protoplasm and which reproduces by budding. It can be easily grown on suitable media as a mycelium which penetrates the medium producing the "inverted pine tree" growth.

Sprue or psilosis is a chronic, afebrile, intestinal disorder due possibly to infection by Monilia psilosis. According to most authorities, however, it is a deficiency disease associated with cirrhosis of the liver, and characterized by a painless, fatty diarrhea of copious, pale, acid stools from which may be recovered almost half of the fat ingested; a sore mouth, the tongue inflamed and often ulcerated or cracked; progressive emaciation; and anemia of the primary type.

The treatment is rest in bed, warmth, protection against all chilling, and a diet so ordered that it produces little fermentation, that is, one free of glucose formers. It should consist at first of increasing amounts of boiled milk, from six to ten pints a day; then the diet is changed to one of fruits, especially strawberries, which seem to have special value in the treatment of this disease; then the patient is given meat juices, and finally much undercooked, lean meat (chopped fine) and at least two quarts of hot water a day.

As regards medication one is advised to avoid acids, bismuth, tannic acid, salol, calomel and any drug which might irritate. Among the medicines recommended are castor oil to clear out the bowel, and powdered ipecac, from 20 to 30 gr. daily, for two or three days. The pain is best controlled by laudanum and adrenalin. The dietary treatment is the best. Ashford and Cantile emphasized the value of the meat diet.

HEMISPORALES

The third order of the **Hyphales**, the HEMISPORALES, reproduce by hemispores. (Hemispores are true reproduction spores called also deuteroconidia. These fungi develop a mycelium composed of abundant hyphæ, which are fine, yet always over 1 micron in diameter, which produce branched conidiophores, each branch terminating in a proconidium, an ampulliform structure which later divides into several sporiform bodies, the deuterospores or hemispores.)

But one family of this order is of interest to us, the HEMISPORACEÆ; and of this but one genus, *HEMISPORA*.

Hemispora rugosa is one of the hemispora which grows on glucose agar, producing an abundant growth with crinkled, occasionally cerebriform surface. Hemispora pararugosa differs from the above only in that it at times produces acidity in milk, which Hemispora rugosa does not.

Bronchitis.—Bronchohemisporasis is an infection of the bronchi and alveolæ due to Hemispora rugosa. This disease occurs not only in the tropics but also in the temperate zones. Mild cases are afebrile, and characterized by cough with mucopurulent expectoration which does not contain blood, and no disturbance of the general condition. The physical examination of the chest is negative, or reveals merely a few coarse râles. The severe type closely resembles phthisis, with emaciation, hectic fever, and bloody expectoration. The physical examination of these patients may reveal patches of dulness, where fine crepitation and a pleural friction rub may be heard.

Tonsillitis.—This organism causes also a tonsillitis characterized by the presence of yellowish or grayish patches.

CONIDIOSPORALES

The organism of the fourth order, the CONIDIOSPORALES, reproduce by conidia. (Conidia are asexual spores, usually round or oval, but some are spirally shaped, which develop from the mycelial threads by processes of budding, septation or abstraction. These may develop from the side—lateral conidia—or ends of the thread—terminal conidia—and may or may not be pedunculated. All conidia are unicellular at first, but later may become pluricellular. The true conidia become easily detached from the thread.) Under this order are four important suborders: (1) the ALEUROSPORINEÆ, which reproduce by aleurospores (or false spores, at first not distinct from the mycelial thread on which they grow, and set free only after the death of that thread); (2) the SPOROTRICHINEÆ, which reproduce by true conidia but without the development of true conidiophores; (3) the SPOROPHALINEÆ, which reproduce by true conidia borne on true conidiophores; and (4) the PHIALIDINEÆ, which reproduce by true conidia borne on phialides (bottle-shaped cells).

Sporotrichosis.—Belonging to the SPOROTRICHINEÆ is the genus SPOROTRICHUM, a well-known example of which is Sporotrichum schenckii, the cause of sporotrichosis. These organisms, when found in smears of the pus from the lesions (which is seldom), appear as oval cells, from 2 to 10 microns long and 1 to 3 microns wide, and frequently engulfed in large mononuclear plagocytes. Grown at room temperature on the surface of Sabouraud's medium or on 4 per cent glucose agar, the colonies appear in not less than four days as minute gray flecks soon surrounded by a delicate fringe. Studied in hanging drop cultures the growth consists of a meshwork of branched septate hyphæ of uniform width (about 2 microns) anywhere along the length of which may develop on short sterigmata the oval or pear-shaped spores which measure about 2 by 3 microns (see Chapter XXV, page 367).

Class II of the Eumycetes, that is, the ***ASCOMYCETES***, develop ascus spores (spores developed in a special sac) and a septate mycelium, if any. Under this class are two orders: the SACCHAROMYCETALES, with asci not gathered into definite perithecia; and the ASPERGILLALES, with asci gathered into globular or cylindrical perithecia.

Of the SACCHAROMYCETALES there are two important families: the SACCHAROMYCETACEÆ, which form no definite mycelium; and the ENDOMYCETACEÆ, the vegetative cells of which do form a definite mycelium.

Several genera of the Saccharomycetaceæ are saprophytes of man. Fungi of the genus Saccharomyces have a vegetative body which in the host consists of budding elements only, but, if grown in cultures, asci develop.

Saccharomyces are found in abundance in the stomach, where they may cause much gas; in the urinary bladder of patients with glycosuria, which sugar they may ferment causing a troublesome pneumaturia; in pulmonary cavities of cases of pulmonary tuberculosis, etc.

The ENDOMYCETACEÆ have two important genera, *ENDOMYCES* and *COCCIDIOIDES.*

Fungi of the genus *ENDOMYCES* are very similar to those of the genus Monilia (see page 389) but with one important difference—that, in old cultures of Endomyces, asci are present.

Endomyces albicans is an organism found in the membrane of thrush. In cultures it develops mycelia which develop spherical chlamydospores, singly or in pairs, at the tips of the threads.

It develops also endoconidia in the mycelial threads, and lateral and terminal exospores. The asci may develop either at the tip or in the course of a thread. These are elliptical or oval in shape, and contain four spores. The delicate membrane quickly disappears.

In the genus *COCCIDIOIDES* some would classify the important pathogenic "yeasts" as Blastomyces hominis and Coccidiodes immitis.

The second family of the BLASTOSPORINEÆ, the OÖSPORACEÆ, contains three important genera: *OÖSPORA, MONILIA* and *OÏDIUM.*

The order ASPERGILLALES contains two important families: the GYMNOASCACEÆ, with growth composed of loose hyphæ and reproduction by mycelium or conidiospores (in which family many would place some of the orders of the Trichophytonaceæ); and the ASPERGILLACEÆ which produce asci generally contained in a globose hollow structure, the perithecium, with a terminal opening or pore, and a compact peridium.

Of the Aspergillaceæ two genera are important: *ASPERGILLUS* and *PENICILLIUM.*

Aspergillus fumigatus is by far the most important of the Aspergillaceæ. Its mycelium is a thick mesh of threads from 3 to 6 microns wide, the youngest without, but the oldest with, septa. All parts of this mold have a brownish or dark grayish-green color. The conidia-bearing hyphæ are short and club-shaped, their larger (distal) end from 8 to 10 microns in diameter. The sterigmata are unbranched, from 6 to 16 microns long, and radiate from one central point, thus giving them a fanlike appearance. The conidia, a chain of which is at the end of each of the sterigmata, are round, colorless and from 2.5 to 3 microns in diameter. (The size of these spores is important, since those of Aspergillus glaucus are from 7 to 8 microns in diameter.) These spores are almost omnipresent.

Aspergillus flavus has conidia-bearing hyphæ which are from 7 to 10 microns thick, and a growth which is yellowish or green in color, according to whether it is dry or wet, and which is brown when old. The conidia themselves are round, of a sulphur-yellow color, and from 5 to 10 microns in diameter.

Aspergillus niger has a chocolate brown color, and conidia which are from 3.5 to 5 microns in diameter.

Aspergillus subfuscus has an olive-green to a black color and strongly resembles the fumigatus, but is more pathogenic.

The best test for the pathogenicity of aspergillus is the intravenous injection of the spores into guinea pigs and birds. If pathogenic, the animals will die in from forty-eight to seventy-two hours.

Aspergillus molds are present as saprophytes in the alimentary canal, especially in the mouth, pharynx and esophagus, but also in the stomach and intestine. They are secondary invaders in tuberculous cavities of the lungs, in bronchitis, etc. But these molds are truly pathogenic and can produce primary infections in those apparently well, but especially under certain conditions such as severe diabetes or extreme cachexias.

Aspergillus may cause a membrane on the mucous membrane of the mouth which superficially may resemble thrush but which will have the color of the mold producing it. The patients thus infected are by no means always infants or feeble adults; quite the contrary. The prognosis of these cases is radically different from thrush, since this infection is most stubborn, resisting for years all forms of therapy.

Conlon reported a case of Aspergillus niger infection of the pharynx of a boy eighteen years old. The whole pharynx and nasopharynx was covered by a tough, black, glistening membrane made up of the mycelium and spores of Aspergillus niger, which could easily be removed, leaving an apparently normal mucous membrane. The patient said that two days before this membrane appeared he had been engaged cleaning a hencoop. In spite of rather vigorous treatment this mold could for weeks be demonstrated in the secretion of the pharynx.

Through the courtesy of Dr. J. F. Barnhill of this University we have been able to study a case of Aspergillus fumigatus infection of the soft palate of a girl sixteen years of age. In July, 1921, because of a continuous throat trouble, this patient's tonsils were removed under general anesthetic. For three weeks she complained of a rawness and soreness on the right side of throat, and at the base of the right pillar one could see a fissurelike ulcer about 10 mm. in length. This was cauterized with pure silver nitrate. It was four months before this ulcer finally healed. In March, 1922, this patient returned, complaining of soreness of her mouth and throat. The entire soft palate, anterior surface, was then found covered with a grayish white membrane which has persisted up to the present time (July, 1923). Her physicians state that they have treated her throat with every remedy known to them but without success. The membrane can with difficulty be wiped off, leaving a raw bleeding surface. Remove it, and in a few hours it will again cover the entire soft palate. Leave it alone, and in from twenty-four to seventy-two hours it will separate completely and another develop. Her general health has been good; her temperature and pulse are normal. It is interesting that her blood Wassermann is reported 100 per cent positive, although her life history as to luetic infection is negative and vigorous antiluetic treatment has not in any way affected the throat condition.

Her red blood-cell count was 4,550,000; hemoglobin 95 per cent; the leukocytes 5,000, of which 62 per cent were polymorphonuclear neutrophils, 22 per cent lymphocytes; 10 per cent large lymphocytes; 2 per cent large mononuclears; 2 per cent transitionals; and 2 per cent eosinophils.

The genus *PENICILLIUM* is characterized by its segmented conidia-bearing hyphæ which divide, brushlike, at the end, the branches of which are tipped by sterigmata which are flask-shaped, bearing conidia from 2 to 3 microns in diameter.

Penicillium glaucum is the most common of our media contaminations, and the commonest in nature of all the Aspergillaceæ. Penicillium nummula is certainly pathogenic for animals, and has been found in the ear of man. We have found Penicillium glaucum in the sputum of two cases of pneumomycosis.

Penicillium montayai is described as one of the causes of pinta (see page 400). Escomel isolated a penicillium from a case of onychomycosis.

The Bronchopneumomycoses

One frequently finds molds in the sputum of patients with tuberculous and bronchiectatic cavities. They are constantly present in the sputum of some cases, however, which have no evidence of these diseases. In these the pulmonary mold infection would seem primary. Formerly all of these "bronchopneumomycoses" were interpreted as secondary mold infections of hemorrhagic infarctions or of pulmonary cavities, from which they had crowded out the primary invader. There would indeed seem to be such an antagonism between molds and the bacteria of decomposition that a cavity filled with the former is protected against the latter, and vice versa. It is of interest that the contents of cavities containing molds are odorless. Now, however, thanks to the work of the French, it seems probable that Aspergillus fumigatus and also, we believe, Penicillium glaucum can as primary invader of the lungs cause "bronchopneumomycosis" and also can cause by necrosis an odorless cavity.

We have reported two cases in the sputum of which Penicillium glaucum only could be found and at least two others which we are confident were infections by Aspergillus fumigatus.

Cases of primary bronchomycosis may for years expectorate grayish, downy masses of mycelium the size of a bean, or even molds of the large bronchi, from 1 to 6 cm. long, formed of mycelium and conidia. These patients usually are grain sorters, millers and gardeners. This chronic bronchitis may later produce a pulmonary fibrosis. These cases expectorate an abundant, foamy, and watery sputum, in which may at times be found casts of the bronchi. Cases of pneumonomycosis aspergillina may develop cirrhosis of the lung or pulmonary cavities. These cases may be "sporadic," affecting old feeble subjects or persons suffering from a lung disease, or "endemic," in which case the disease is due to the occupation of the patient.

In other cases the disease takes the form of a pseudotuberculosis. This is best seen in pigeon feeders who expose themselves to the molds of grain by allowing the young birds to feed the masticated food directly out of their mouths, and in those who use meal to comb out hair, and those who clean sponges. The course of this disease resembles chronic pulmonary tuberculosis. At the onset there often is recurring hemorrhage, either slight or profuse, and a cough which at first is dry but later is accompanied by a frothy sputum which quickly becomes greenish in color and purulent, and which often contains blood flecks. This may continue for years. Later, after definite cavities have formed, the sputum is a greenish pus which often contains blood and which is expectorated in nummular masses.

Diagnosis.—For the *diagnosis* of a pneumomycosis one must demonstrate in the sputum either the mycelium, the conidia hyphæ, or the spores of the mold and, second, must by every means available exclude tuberculosis. As a rule, the mold threads and spores in sputum are either overlooked or are passed by as extraneous. The sputum must be obtained under as aseptic precautions as possible, then washed several times with sterile water, and then examined fresh. An odorless sputum is always suggestive of mold infection. This is particularly striking in cases of gangrene of the lung and of all cases with large masses of lung tissue in the sputum. The possibility of tuberculosis should if possible be excluded by the history of the case, with special reference to the family history, to the presence in the past history of enlarged glands and of pleurisy, either fibrinous or with effusion; by the absence of Bacillus tuberculosis in the sputum, proved not only by repeated negative bacterioscopic examinations but also by negative cultures of the sputum and by the negative results of repeated injection of the fresh sputum into guinea pigs; by the negative reports of the various tuberculin reactions; and by the absence of fixation of complement for tuberculosis by the patient's blood.

The roentgenograms of the chests of these patients are very suggestive, sometimes even conclusive. One notes an absence of calcified glands or of calcified scars at the hila of the lungs; both apices are relatively clear and certainly are free from shadows suggesting tuberculosis; there is at the hilum of one or both of the lungs a dense shadow which radiates in coarse lines usually into one lobe only, and which spreads out peripherally into a diffuse infiltration, the appearance of which suggests sometimes a bunch of grapes. One sees no typical ramifying and anastomosing thickened bronchial markings; no nodes along the bronchi, etc.

History.—The clinical history of these cases is very suggestive. They have had their lung troubles for years and usually have for years been considered tuberculous. Two of my patients have been treated several times in sanitariums for the tuberculous. Their general health has been little if at all impaired; they have not lost appreciably in weight or strength; they are not anemic; they have been almost afebrile; they have had no malaise.

Their local symptoms, on the other hand, are extreme. One of our patients, a man forty-seven years old, had had for years bad smothering spells, clearly of intratracheal origin, so severe that he "felt he would choke to death," and which required morphin for their relief. For several years he had been obliged to sleep in a chair, and yet each day could do a hard day's work. The pulmonary signs on inspection, palpation and percussion suggest fibroid phthisis, but those on auscultation suggest a serious, rapidly extending, general tuberculosis. It is positively uncanny to listen to the multitudes of râles in the chest of patients so little sick.

These cases may be much more common than we believe. It is interesting that Castellani reported that, of all the Italian soldiers referred to him during the past War for pulmonary tuberculosis, at least 3 per cent were cases with mycosis or sporochetosis of the bronchi. Nathan evidently had the same opinion, for he says that many cases of so-called pulmonary tuberculosis are mold infections but that the mistake is not discovered since these patients are placed in hospitals for the tuberculous, where they soon contract that disease.

Treatment.—The treatment of these bronchomycoses and pneumomycoses is quite unsatisfactory. By means of potassium iodid in large and increasing doses they improve but do not recover. One of our cases, a man who for six years had been unable to work, not because of weakness but because of the severity of his attacks of dyspnea, was able, soon after beginning the increasing doses of potassium iodid, to drop his morphia and to resume work. He is by no means well for he still has some dyspnea on exertion and some cough, but for the past nine years he has been able to support himself and has lost practically none of his time at work.

Another of our patients, a woman, improved much under potassium iodid, but did not recover. Dr. Max Rothschild, under whose care she now is, after thorough trial of partial antigens prepared from the cultures of mold from her sputum, treated her with arsphenamine injections but without results. He therefore prescribed daily inhalations of turpentine vapors. Her general condition is decidedly better and her cough and sputum decidedly less.

Unfortunately no serological treatment of mold infections is at present possible since there is no evidence that any immunity reaction develops. Mr. Forry of our pathological department attempted, by injecting increasing doses of a suspension of the mold spores, to immunize rabbits to molds, but was unable later to demonstrate in their blood the presence of any complement-binding body.

Pinta, due to Aspergillus pictor, is a contagious skin affection found only in the tropical regions of Mexico and South America, which is characterized by the appearance of black, red, violet and white (their color depending on their age) scaly patches on the skin, especially of the exposed surfaces, which apparently are spread by scratching. These patches have been shown to be due to various fungi, of which Aspergillus pictor, Penicillium montayai, Montoyella, and Monilia are the best known. The patches are usually first noted on the face and neck or hands and feet but not on the palms and soles; itching is marked. The diagnosis can be made from the examination of scrapings in liquor potassii, and by the cultivation of the fungus on Sabouraud's medium.

Finally, Class IV of the Eumycetes, the ***PHYCOMYCETES,*** are characterized by their continuous non-septate mycelium threads. This class has but one important order, MUCORALES, the asexual spores of which are developed in sporangia. One family only of this order, the MUCORACEÆ (with columella present in sporangium), is important. These Mucoraceæ produce a branching mycelium with aërial branches (gonidiophores) each of which supports on its distal end a globular, pear-shaped or claviform sporangium (gonidiangium) which at first is separated from the gonidiophore by a septum. This septum later protrudes into the sporangium and becomes the columella. The conidia develop in the sporangium by free cell division and later are set free by the bursting of the sporangium membrane. Of the Mucoraceæ there are four genera members which are pathogenic to man: *MUCOR,* with mycelium ramified, and rhizoids (slender rootlike filaments) absent; *RHIZOMUCOR,* with rhizoids present, and columella ovoid; *RHIZOPUS,* with rhizoids present and columella mushroomlike; and *LICHTHEIMIA,* with peduncle supporting sporangium which ends in special formation encircling the base of the columella.

MUCOR has one hundred and thirty varieties, of which six are known to be pathogenic. These are Mucor corymbifer, a fine, delicate, small mold with spores 2 by 3 microns in diameter, and sporangia which are colorless, pear-shaped, which vary in size from 10 to 70 microns, and have a transparent membrane. The columella, evident only after it is free of the spores, is top-shaped, its large distal end colorless. This form has been found perhaps most often in man as the cause of keratomycosis, otomycosis, pharyngomycosis, and pneumomycosis. Mucor rhizopodiformis, has sporangia-bearing hyphæ which are single or branch sheaflike and which are short and brown in color. The sporangia are globular, black when ripe, with an opaque membrane which is soluble in water, and brownish columella which is constricted at the base, truncated, and has a wide (50 to 75 microns) flat apophysis, to the margin of which the membrane is attached. The spores are colorless, spherical, and from 5 to 6 microns in diameter. The spores of Mucor racemosus are oval from 5 to 8 microns long and 4 to 5 microns wide. The columella is elliptical in shape. Mucor pusillus has black sporangia with a thorny membrane, which are from 60 to 80 microns wide; a columella which is egg-shaped or spherical, light brown in color and from 50 to 60 microns wide; and spores which are very small, from 3 to 3.5 microns in diameter, round and colorless. Mucor septatus has a pale, grayish brown, spherical sporangium, small colorless columella which, after the loss of the spores, may grow still further. The hyphæ have septa, hence the name. The spores are about 2.5 microns in diameter. It has been found in the ear. Mucor ramosus has black sporangia which measure 70 microns in diameter, and which have a transparent membrane. Its columella is round and the colorless and opaque spores from 3 to 4 microns wide and 5 to 6 microns long.

These forms of Mucor are known to be pathogenic; they invade the skin (dermatomycosis); almost all of them have been demonstrated in the ear (otomycosis) in the external auditory meatus, the most common seat of infection, in which they form masses made up of inflammatory exudate, cerumen and desquamated cells. They infect the nose (rhinomycosis), and may penetrate and cause necrosis of the cornea of the eye. Cases of Mucor enteritis have been reported while one case of general infection by Mucor corymbifer involved the intestinal wall and produced multiple abscesses throughout the body, including the brain and lungs. Only four cases have been reported in which Mucor molds have been demonstrated in the lung.

Otitis Externa Parasitica

Although any infection is a parasitic disease, yet otitis externa parasitica is the term formerly in common use for the conditions now referred to as otomycosis, or infection of the external ear by fungi which belong to the aspergillus and mucor groups. In general otological practice these otomycoses make up from $1/10$ to 1 per cent of all cases. Many of these cases have had a previous otitis, especially of the circumscribed external type. It is rarely if ever found with purulent otitis. It is frequently associated with diabetes mellitus perhaps because of the aural pruritus so common is this disease which leads to scratching, pulling, rubbing of the ear and so to slight local injuries in the canal which make mold infections possible. Burnett was of the opinion that they were met with most often in the autumn, and especially among those who dwell in dark or damp apartments. He says that it is not uncommon for several in the same apartment to be affected. Many of the patients are from rural districts. The prevalence of this condition among the upper classes is due to the tendency of these persons to use various drops for their ear conditions. He suggests that the physicians who use dirty instruments or prescribe fatty aural applications are responsible for some cases. It is rare in the aged and in the young.

The macroscopic signs on examination are unmistakable. On inspecting the fundus of the canal of an early case there is injection of the myringeal plexus and a visible veil-like plaque of mycelium on the drum head. Later the inner end or sometimes the whole of the wall of the canal and the drum head are covered with a substance resembling wet newspaper or dirty blotting paper, on which are tiny raised spots, black, brown, green or yellow in color. The serous effusion also present is sometimes so profuse as to fill the canal. This pseudomembrane may be mistaken for a foreign body, for a laminated epithelial plug, for diphtheritic otitis media or for cerumen. After removing this pseudomembrane, the exposed corium looks raw and produces a profuse exudate. Forcible removing of this membrane leaves a bleeding surface. There are no constitutional disturbances as would be the case in diphtheria. A laminated epithelial plug or keratosis obturans is not moist as the fungus growth, and is made of layer upon layer of epithelial tissue which can readily be distinguished under the microscope. A small specimen is easily removed for cultural study and microscopic examination will reveal the fungus at once.

The prognosis of recovery is good but recurrences are frequent. One single treatment may affect a permanent cure provided the drum membrane is intact. If, however, this is perforated and the fungus is growing within the middle ear, then cure is difficult unless the ear drum first heals.

Treatment.—In most cases careful spraying with warm sterile water or alcohol will bring away most of the growth. While the part of the growth intimately attached to the tissues can be removed by gently wiping the surface with a brush of cotton wool rolled on the end of a cotton carrier, yet it is better to use a germicidal preparation first and then to remove the entire growth by syringing. All oily exudate must first be removed by syringing with an alkaline solution of 2 per cent salicylic acid in alcohol. Among the local applications alcohol is popular. Dr. Burnett has recommended a powder which consists of chinolin salicylate 1 part and boracic acid 16 parts. Another prescription is:

℞	Acid. acet. dilut.	♏ 6
	Liq. plumbi subacetat.	♏ 20
	Liq. opii sedativa	♏ 20
	Distilled water q. d.	

Add ounces 1, dose 10 drops, warmed, in the ear.

Some use alcohol only. Others use solutions of tannin, mercuric bichlorid, lead salts, carbolic acid, 2 gr. to the ounce, or silver nitrate 10 or more gr. to the ounce.

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INFECTIONS DUE TO PROTOZOA

CHAPTER XXIX

MALARIA

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Malaria is an infectious disease caused by animal parasites of the class Sporozoa, genus plasmodium, whose definitive host is the anopheline mosquito and whose intermediate host is man. In man these parasites enter and destroy the red blood-cells, giving rise to anemia and other pathologic lesions and upon sporulation produce fever and other symptoms, the chief characteristic of which is periodicity.

Mosquitoes do not cause malaria; they carry it from infected to healthy persons. The parasites, sucked with blood from a malarial individual, undergo a cycle of development within the body of the mosquito, and are then inoculated into healthy persons. Man is merely the intermediate host of the parasite, the mosquito is the definitive host, and it may be said that man gives malaria to the mosquito, rather than the mosquito to man.

Not all species of mosquitoes can serve as hosts for the malaria parasite. It is only certain members of the subfamily Anophelinæ that have been found to act in this capacity. Of this family about forty-four members have been determined, with more or less certainty, to be malaria carriers and of these about four are indigenous to the United States.

The relation of the mosquito to malaria explains the prevalence of the latter with reference to season, temperature, and rainfall. It explains malaria as a disease chiefly of low altitudes and marshy regions; a disease of the country rather than of the city. House epidemics of malaria are thus rendered clear and the relation of ship malaria and proximity to the shore becomes obvious. The bearing of age, sex and occupation upon the endemic is in thorough harmony with the theory. That malaria is more easily contracted at night is understood from the feeding habits of the malaria-bearing mosquitoes. That all measures directed toward the prevention of mosquito bites are followed by a commensurate reduction of the prevalence of malaria is one of the most conclusive arguments. Numerous and accurate experiments have absolutely proved the dissemination of malaria by certain mosquitoes and the sexual cycle of the parasite within the mosquito has been followed many times.

The parasites of malaria belong to the animal kingdom, to the division of Protozoa, to the class of Sporozoa and to the order of Hæmosporidia.

There are three sharply defined species of malaria parasites: the parasite of tertian malaria, the parasite of quartan malaria, and the parasite of estivo-autumnal malaria. The latter may be divided into two varieties: the tertian and the quotidian, of which latter variety a pigmented and an unpigmented form are described.

The life history of the parasites of malaria is somewhat complicated, inasmuch as man, the mosquito, and the parasite are involved, and as there are three species of parasites and each species has three biologic cycles. These three cycles are:

1. The schizogonic, or human cycle, also called the asexual cycle, monogonic cycle, endogenous cycle or trophic cycle.
2. The sporogonic or mosquito cycle, also called the sexual cycle, amphigonic cycle, or exogenous cycle.
3. The parthenogenetic cycle, or reproduction by unfertilized macrogametes, the cycle of chronic malaria, of latency and relapses.

THE SCHIZOGONIC CYCLE

In the act of biting the mosquito injects into the blood sporozoïtes, elongated or needle-shaped organisms, each of which immediately penetrates into a red blood-cell where it loses its slender form and appears as a mere dot of protoplasm about 1 or 2 microns in diameter. Ameboid motion is more or less active and as the parasite grows it acquires pigment from the hemoglobin of the infested cell, occurring in the form of grains, rods or clumps. The adult parasite occupies a relatively large portion of the cell and ameboid motion is less active, though the pigment may be in violent motion. Prior to sporulation the pigment becomes concentrated and fused, and fission occurs, dividing the parasite more or less symmetrically into spores, constituting the so-called rosette or marguerite forms, each spore containing a fragment of nucleus. The cell ruptures and the spores, or merozoites, escape into the blood current where they rapidly enter the red blood-cells to repeat the cycle. Instead of proceeding to sporulation, some of the parasites develop into sexual forms, or gametes, large parasites of round, ovoid, or crescentic shape. It is these bodies which are taken up by the mosquito, undergo a cycle in its midgut and develop into sporozoïtes which are injected into man where they pass into the schizogonic cycle above outlined. The duration of the asexual cycle of the simple tertian parasite (Hæmamœba vivax, Hæmamœba tertianæ, Plasmodium vivax) is forty-eight hours. The young parasites are actively ameboid, the pigment is fine, rod-shaped, rather light in color, and in active motion which has been compared to the bubbling of boiling water or to the swarming of insects. The infested red cell becomes enlarged, swollen and pale. The half-grown parasite assumes fantastic and bizarre shapes, while the adult is more or less spherical and occupies the greater part of the swollen cell. The sporulating tertian parasite is not so symmetrical as the corresponding stage of the quartan. The spores are small and vary in number from twelve to twenty-six, most often sixteen. Sporulating tertian parasites are much more frequently encountered in the peripheral circulation than is the case with estivo-autumnal infections.

An interesting phenomenon occurring in the case of the male sexual forms is exflagellation. The flagella are now known to be spermatozoa.

In stained films the early stage of the tertian parasite is seen as a ring, set with a chromatin dot. The forms of half-grown parasites are of various and peculiar shapes. The red cell is enlarged and does not stain deeply.

The duration of the schizogonic cycle of the quartan parasite (Hæmamœba malariæ, Hæmamœba quartanæ, Plasmodium malariæ, Laverania malariæ) is seventy-two hours. The young forms are more highly refractive, their ameboid motion more sluggish, their pigment in larger quantity and in coarser grains and of deeper color than in the tertian parasite.

The red blood-cell does not enlarge and decolorize as in tertian infections, but is apt to be smaller and darker, perhaps greenish and brassy. The adult parasites are almost the size of the red cells and the sporulating forms are beautifully symmetrical and often typical rosettes. The spores are relatively large and six to twelve in number, most often eight. The staining reactions of the quartan parasites are similar to those of the tertian.

The young forms of the estivo-autumnal parasites (Hæmamœba præcox, Plasmodium præcox, Plasmodium falciparum) are from one-fifth to one-sixth the size of the infested corpuscle. Ameboid motion is rather active. Advanced forms of development are rarely found in the peripheral circulation. The infested red cells often become shriveled and are of a darker shade. The adult parasites are smaller than red blood-corpuscles and sporulation takes place in a manner similar to that of the simple tertian parasite. The spores number from five to about twenty-five or thirty. Gametes occur in the form of crescentic, fusiform, ovoid, or spherical bodies. In stained specimens the young unpigmented ring bodies are smaller and more delicate than the simple tertian parasite.

For a consideration of the sporogonic and parthenogenetic cycle the reader is referred to the monographs on malaria.

The parasites of tertian and quartan infections develop uniformly, one generation at a time, hence typical paroxysms are the rule. The estivo-autumnal parasites, on the other hand, do not develop so uniformly, hence the poison is liberated in broken doses and typical paroxysms are more frequently lacking, the fever being more nearly continuous or irregular.

Of the pathogenic factors which excite pernicious symptoms the following are to be regarded as the most important and approximately of relatively equal importance: (1) an excessive number of parasites; (2) intensive localizations of parasites; (3) toxins; (4) individual predisposition and external etiological influences.

The period of incubation of malaria varies within very wide limits. The average period is, for quartan, twelve to eighteen days; tertian, six to fourteen days; estivo-autumnal, two to ten days.

The active paroxysm may be preceded by several hours, or a few days, by languor, anorexia, headache, aching of the loins and hips, thirst, epigastric distress, a disposition to yawn and stretch and a chilliness along the course of the spine. The typical malarial paroxysm comprises three well-marked stages: the cold stage, the hot stage and the sweating stage. The sensation of coldness spreads over the body, the skin becomes pale, the patient shivers, covers up and his teeth chatter. Notwithstanding these evidences of cold the thermometer shows an elevation of internal temperature. Headache, backache, precordial oppression, and dyspnea are frequent complaints and the patient may suffer with nausea and vomiting. The cold stage may last from a few minutes to two or three hours. With the onset of the hot stage, hot flashes alternate with cold until the sense of heat becomes general, the patient begins to uncover, the skin is flushed and hot, respiration becomes deeper, the urine is scanty and high colored. There may be constipation or diarrhea. Facial herpes is commonly seen. The spleen is enlarged and the upper half of the abdomen is tender on pressure. When the temperature is at its highest, the sweating stage is ushered in by crisis. The temperature falls to normal or below, the pulse and respiration resume their normal features, the discomfort disappears and the patient often feels so much relief that he takes a short nap. In some paroxyms the cold stage is absent and the sweating stage may be inconspicious. Anemia is usually in proportion to the duration and severity of the attack.

Infection with a single brood of simple tertian parasites causes a paroxysm every other day. With two broods, a double infection with two distinct generations of parasites, maturing on alternate days, the paroxysms are quotidian. There is usually a perceptible difference between the paroxysm of succeeding days, a difference consisting of time of onset, severity and relative length of the stages of the paroxysm.

The quartan parasite accomplishes its endogenous cycle in seventy-two hours. Infection with a single generation of quartan parasite, therefore, produces a paroxysm, followed by two days of apyrexia and a second paroxysm on the fourth day. A double quartan infection causes two paroxysms on succeeding days, followed by a day of apyrexia. Triple quartan infections, the parasites maturing on succeeding days, give rise to quotidian fever.

In infections with the estivo-autumnal parasite the clinical course is very irregular as compared with that of tertian and quartan infections. The most frequent variety of the so-called pernicious malaria is the comatose. Usually after the course of two or more paroxysms, violent headaches, stupid countenance and somnolence supervene and coma ensues.

In the algid type the first symptoms that attract attention are the bad pulse and cold surface. The body is bathed with a clammy sweat and prostration is extreme. The patient complains of burning heat inside though the temperature may be subnormal or only slightly elevated. The pulse is rapid and filiform, and the respiration is rapid and superficial. The bowels are sometimes constipated, but usually loose.

Chronic malaria consists of a latent or passive stage and an active stage or the stage of relapse. The latent period resembles in some respects the period of incubation; the symptoms may be insignificant or altogether absent. Relapses occur at shorter and at longer intervals. The duration of the shorter intervals show a tendency to septenary periods.

Masked malaria is merely atypical malaria, with nervous, gastro-intestinal or cutaneous disorders predominating.

Malarial cachexia is a sequel of chronic malarial infection. The cachectic usually has emaciated limbs, which are in marked contrast to the distended abdomen, and the features are aged beyond the years. The most pronounced phenomena are the anemia and the enlarged spleen. Parasites are not regularly found in the peripheral blood. The stained film shows marked evidences of a secondary anemia and there may be a large mononuclear leukocytosis. The spleen often extends from the umbilicus to the crest of the ilium, sometimes beyond. It is usually hard and the anterior border presents a sharp edge.

The three sources from which information may be drawn to make a diagnosis are: (1) from the symptoms; (2) from the examination of the blood; (3) from the effect of quinin upon the symptoms.

Of the clinical history the most important feature to be considered is periodicity. Tertian and quartan periodicity are pathognomonic of malaria. Quotidian periodicity is not only worthless but sometimes actually misleading in the diagnosis of malaria.

Stained films of the blood have a wider margin of usefulness to the general practitioner than preparations of the fresh blood. The films are fixed in absolute methyl alcohol for about a minute. The following stain is freshly mixed, poured on and allowed to remain ten to fifteen minutes: watery eosin in water, 1:500, 10 drops; azure II in water, 1:500, 10 drops; distilled water, 30 drops. The film is then washed in distilled water and dried with filter paper. Cedar oil is placed directly on the film without the use of a cover glass. Several examinations are sometimes necessary before the parasites can be found and previous administration of quinin usually renders their detection impossible.

A fever which resists quinin is not a malarial fever unless it be one of the pernicious forms. In most cases the fever is broken at the end of thirty-six hours, and if resistant to quinin longer than four days is probably not malaria. It is of course essential that the specific be absorbed.

TREATMENT

Quinin is now regarded as a specific for malaria; however, it has its limitations. A radical cure is sometimes difficult, certain cases of pernicious malaria are not influenced by it and some of the sequelæ are difficult to control.

The following table shows the alkaloid strength of the various salts of quinin and their solubility:

Alkaloid Strength of Quinin Salts and Their Solubility

Salt	Per Cent of Alkaloid	Solubility in Parts of Water
Quinin, anhydrous	100	1,750
Quinin acetate	84	Slightly
Quinin dihydrochlorid (acid hydrochlorid)	71	Less than its weight
Quinin bisulphate	59	8.5
Quinin citrate	67	820
Quinin hydrobromid	76	40
Quinin lactate	78	10
Quinin hydrochlorid	81	18
Quinin salicylate	68	77
Quinin sulphate	74	720
Quinin tannate	About 30	800
Quinin valerianate	76	53
Euchinin	81	12,500

Most of the salts are readily absorbed from the stomach and appear in the urine from fifteen to forty-five minutes after administration. The tannate, however, is more largely absorbed from the small intestine and does not appear in the urine for about three hours after oral administration. With the more soluble salts elimination takes place in the greatest quantity within three to twelve hours. Quinin is more slowly absorbed from a full than from a fasting stomach and it has been found that elimination by the urine is about one-sixth longer when administered in five daily doses than in a single dose.

Coagulation and precipitation always follow the injection of concentrated solutions of quinin into the tissues, resulting in a slower absorption and decreased elimination. After intravenous administration quinin has been detected in the urine within ten minutes. After injection in the rectum it appears in the urine in from twenty to twenty-five minutes. Besides elimination in the urine, quinin is excreted with the feces, the milk, the tears, pathologic transudates and exudates, the amniotic fluid and the first urine voided by the newborn children of cinchonized mothers.

It was shown in 1881 by Laveran that the parasites were killed by the addition of a 1:10,000 solution of quinin and he concluded that "it is because it destroys the parasites that quinin causes the disappearance of the manifestations of paludism."

The sexual forms of the malaria parasites are very resistant to quinin, persisting in the blood for weeks and months despite the repeated use of the specific.

The stage of the parasite most susceptible to the action of quinin is the merozoit, the spore, before it has assumed the protection of the red blood-cell. Hence it is desirable to have in the blood as strong a solution of quinin as possible at the time of sporulation so that the young parasites may be born into a toxic medium.

The mere statement of the patient that he is unable to take quinin should constitute no bar to its use. However, cardiac depression and dyspnea occurring in very rare instances are decided contra-indications to the administration of the drug. The treatment of malaria complicating pregnancy is essentially the same as under other conditions. The pregnant patient runs far less risk of abortion with rational quinin treatment than without. A history of hemoglobinuric fever is no contra-indication to the use of quinin. While the administration of the drug is sometimes the occasion of an outbreak of blackwater fever, the latter is generally due to too little quinin rather than to too much.

The choice of preparation of quinin is influenced by the age of the patient, the mode of administration, the severity of the attack, and other features. The sulphate is widely employed but it gives rise to more gastro-intestinal and nervous distress than some of the other salts. The bisulphate, the hydrobromid and the hydrochlorid are useful preparations, being easily dissolved and readily absorbed. The dihydrochlorid is the most valuable salt of quinin. Its great solubility adapts it for solution to be given by mouth, by rectum, intramuscularly, or intravenously. Quinin ethyl carbonate, euchinin, has given satisfactory results and being practically tasteless it is easily administered, either in powder, or suspended in a neutral syrup, to children.

The tannate of quinin is a more useful salt than hitherto regarded. Some of its advantages are that it is well tolerated by the gastro-intestinal tract, that the clinical results are entirely satisfactory, that being nearly tasteless it is especially adapted to the treatment of malaria in children and that it has a good effect upon diarrhea and dysentery complicating malaria.

In benign malaria the administration of quinin by the mouth is the rule. Unquestionably the most reliable form in which to give quinin by mouth is in solution, but, for obvious reasons, it cannot be extensively employed in this manner. The solution is quickly and completely absorbed. The dihydrochlorid and the bisulphate are the salts most suitable for solution but the sulphate may be employed by adding a drop of dilute hydrochloric or sulphuric acid for each grain of the quinin. The most effective vehicle for disguising the taste of the sulphate of quinin is yerba santa. Two grains of quinin to the dram of syrup is the suitable proportion.

Pills and tablets are convenient to administer and not unpleasant to take but cannot be relied upon. The coating over them often becomes so hard as to make solution difficult or impossible. Capsules, when fresh, dissolve readily. If there is any doubt as to their solubility they may be punctured several times in each end with a pin or may be followed by a few drops of a dilute mineral acid.

Quinin should not be administered hypodermically since nodules, necrosis, sloughing and abscess are very prone to follow. Quinin may be administered intramuscularly if two important factors are observed: first, asepsis; second, dilute solutions. Strong solutions of quinin injected into the tissues cause a wall of necrosis around the solution, preventing absorption and paralyzing phagocytosis, resulting, even if the solution is sterile, in nodes and ugly chemical sloughs. Under no circumstances should the solution be more concentrated than 1 gm. to 10 c.c. The injection is usually made in the gluteal region and away from large nerve trunks. The preferable salt is the dihydrochlorid. The dose is ordinarily 10 or 15 gr. for an adult.

The intravenous method of administering quinin in malaria has practically superseded the intramuscular route, in fact, the latter method should be resorted to only in those cases of pernicious malaria where it is impossible to enter a vein. The intravenous method is demanded in cases of the pernicious type, where coma prevents oral administration or dangerous symptoms necessitate immediate therapeutic effect; in severe cases in which vomiting prevents retention in the stomach when given by mouth, and in cases in which hyperpyrexia is present without other dangerous symptoms. No special preparation of the patient is necessary preceding an intravenous injection of quinin. Either the gravity or the syringe method may be used. Used by gravity in dilute solutions the rate of injection may be controlled and phlebitis is less likely to occur. In general practice, however, the syringe method has a wide field of usefulness. The water used for the intravenous injection of quinin should be freshly distilled and sterilized. The lack of freshly distilled water should not, however, prevent the use of the specific by this method in urgent cases of pernicious malaria. In such cases the purest possible water should be obtained, filtered, and sterilized.

The only salt of quinin with which I have had any experience by the intravenous method is the dihydrochlorid. The dilution when given by the gravity method should be from 50 to 100 c.c. When the syringe is employed it should be not less than 20 c.c. When the solution is freshly prepared from the powdered salt sterilization is necessary. This may be effected by boiling or autoclaving.

The most frequent reaction following the intravenous administration of quinin is a fall of blood-pressure. This fall may vary from a few millimeters to such an extent that the patient may become pulseless. Rapid injection is the most potent factor determining such changes in the blood-pressure. The subjective sensations of intravenous cinchonization are felt soon after the solution begins to enter the circulation, but these manifestations, with the exception of the roaring in the head, soon disappear.

In patients with pernicious malaria the specific should be administered intravenously without regard to the stage of the development of the parasites. The injections should be repeated every six or eight hours as long as these symptoms persist. Under these circumstances the adult dose should be not less than 20 gr. After the dangerous symptoms have abated the dose may be reduced to 15 gr. at suitable intervals.

Rectal administration may be used as an adjuvant to the intravenous method in pernicious cases. A soluble salt should be used, preferably the dihydrochlorid. The water should be about the temperature of the body, and should not exceed a few ounces in quantity. Ten or 15 drops of tincture of opium should be added to prevent tenesmus and aid retention.

The use of quinin mixed with fats and oils and rubbed into the skin is not to be relied upon, since little, if any, quinin is absorbed by this method.

With reference to the time when the drug is given, there are three chief modes of giving quinin: (1) the method of Torti, a single dose before the paroxysm; (2) the method of Sydenham, a single dose in the decline of the paroxysm; and (3) the method of fractional doses. The first two methods are adapted only to the benign infections.

The efficacy of the method of Torti rests upon the fact that the parasites are most susceptible to the action of quinin immediately after sporulation, while free, before having entered the red cells. It presupposes an accurate knowledge of the hour at which the next paroxysm will occur, based obviously upon a definite history of repeated paroxysms, a temperature chart, or blood examinations sufficiently accurate to determine not only the type of the organism, but its exact stage. It is evident that in private practice, in the patient seen in the first access, the prediction of the next paroxysm must usually depend upon the result of the examination of the blood, and that this must be repeated if the stage is not recognized at the first examination. Unless this can be done quinin should not be administered in this way, for, even if the type of malaria present is known, there are two conditions which may render the single dose futile: first, anticipation of the paroxysm; second, a multiple infection. Even where the blood is carefully examined, it may happen, in double infections, that only one group can be detected in the peripheral blood.

By this method, also known as the Roman method, the quinin is given in a single dose of about 15 gr. from four to six hours before the next succeeding paroxysm. This paroxysm is not prevented; in fact, it may be entirely unmodified; but such a dose, properly timed, usually secures apyrexia subsequently for several days.

In double tertian infections a single dose given in this way may change the quotidian paroxysms into tertian and quartan infections, constituting a sort of fractional sterilization of the blood.

The method of Sydenham, the English method, consists of a single dose, averaging 15 gr., giving in the sweating stage or the decline of the paroxysm. This dose usually prevents succeeding paroxysms; if one should occur it is usually abortive.

The third method, that of small doses at frequent intervals, has numerous advantages over the one-dose methods.

1. Quinin given in this way is better borne by the digestive and nervous systems.
2. The loss of one dose by vomiting or failure of absorption is not of so much importance.
3. The method is adapted to tertian, quartan, or estivo-autumnal infections; this is important, for sometimes these cannot be differentiated clinically.
4. It is adapted especially to estivo-autumnal infections where sporulation is not so nearly synchronous.
5. The time of administration is not dependent on parasitic findings or definite stages, both of which may be obscure where the patient has previously taken quinin.
6. An experience in many hundreds of cases has proved its value.

I have had a large experience with this latter method and have found it very satisfactory. The average dose is 1 gr. an hour, given usually 2 gr. every two hours, 3 gr. every three hours, or 4 gr. every four hours day and night. It is especially important that the drug be given during the night, since thus only may the blood be charged during the day, when sporulation usually occurs.

It is not necessary to defer or discontinue the use of quinin on account of fever, as is believed by some. More than fourscore years ago Maillot showed that to withhold the drug for this reason was not only useless, but dangerous.

Cinchonism is no guide to the quantity to be given; it is not the patient against whom the quinin is directed, but the parasites.

The specific should not discontinued as soon as the temperature is, normal but should be kept up for at least from twenty-four to thirty-six hours longer in the quantity employed during the fever. My method consists, then, in discontinuing the specific for twenty-four hours and giving 15 gr. a day for two days, discontinuing for two days, giving quinin, 15 gr. a day, for two days, discontinuing for three days, giving the specific again, 15 gr., on two successive days and so on increasing the interval by one day following each two-day administration until five days are skipped, after which 15 gr. are given on each of two successive days of each week. This intermittent treatment should be continued at least two months.

The standard treatment adopted by the National Malaria Committee is as follows: For the acute attack 10 gr. of quinin sulphate by mouth three times a day for a period of at least three or four days to be followed by 10 gr. every night before retiring for a period of eight weeks. For infected persons not having acute symptoms at the time only the eight weeks' treatment is required.

Nothing is more discouraging to the physician than the treatment of cachectics in whom the poor hygienic conditions cannot be corrected, which is not rarely the case. The two chief principles involved in the treatment of cachexia are: (1) the prevention of active outbreaks of malaria; and (2) the improvement of the general condition of the patient by appropriate hygiene.

Quinin is most effectively given upon two successive days in each week, as described. This alone, however, will rarely effect a cure except in the mildest cases.

Where it is practicable a complete change of climate should be advised. Without this very little can be accomplished for cases of severe degree. A wholesome, nutritious, and digestible diet should be prescribed. The digestion is often impaired and stomachic tonics may be indicated. Exposure to inclement weather must be avoided on account of the dangers of pneumonia. Occupations which subject the cachectic to violent exertion or to bodily harm should be interdicted for fear of rupture of the spleen. Regular hours must be kept with adequate sleep, and constipation must be overcome.

Of drugs other than quinin, arsenic has the best reputation. It should be given in rather large doses of the arsenous acid or Fowler's or Donovan's solutions.

Iron is nearly always indicated; the organic preparations of iron and manganese are usually well borne by the stomach. The pill of Blaud's mass, 2½ gr., may be tried, or the classic antimalarial pill of iron, quinin, arsenic and strychnin.

Injections of medicaments directly into the spleen, as sometimes advised, are unjustifiable.

Counterirritation over the splenic area may aid in the reduction of the enlarged spleen. The best agent is the ointment of the red iodid of mercury. A piece the size of a pea or larger should be thoroughly rubbed in, the splenic region being bared to the sun's rays or to the heat of a fire. This should be repeated daily until the skin becomes so irritated as to make friction painful, when it should be discontinued, to be resumed again when the condition of the skin will permit. Iodin, turpentine, mustard, firing with the actual cautery, and other counterirritants have been recommended.

In the treatment of malaria in children it is my practice to administer the quinin at short intervals every two or three hours.

While children bear quinin in relatively larger doses than adults, the size of the dose should be regulated by the severity of the attack and the age of the patient. In average cases children from one-half to two years of age may be given from ½ to 1 gr. of quinin every three hours, from three to five years from 1 to 2 gr., and from six to ten years from 2 to 2½ gr. These quantities may be increased in severe attacks.

The drug is ordinarily given by the mouth. Where capsules cannot be used, recourse must be had to a tasteless preparation or to a disguising vehicle. Euchinin and the tannate of quinin are the best of the tasteless preparations. The former must be given in slightly larger doses, the latter up to double the doses indicated above. The most efficient liquid for disguising the taste of quinin sulphate is the syrup of yerba santa, at least 1 dram of which should be given for each 2 gr. of the quinin. In cases with pernicious symptoms the drug should, of course, be injected intravenously or intramuscularly. Rectal administration of a solution or suppository may be employed to supplement other modes. The buttocks should be pressed together for half an hour after insertion to aid retention.

Calomel, mercury with chalk, and castor oil are efficient purgatives in the treatment of malaria in children.

In the treatment of malaria there is no drug that can compare in efficacy to the salts of quinin, nevertheless, in rare instances, it becomes necessary either on account of an idiosyncracy of the patient or a state of resistance of the parasites, termed "quinin-fast," to resort to the use of other remedial agents.

Arsphenamin and neo-arsphenamin have been given a thorough trial in all forms of malaria. The only form in which they are of service is the tertian. In these cases they cause a disappearance of the parasites from the superficial circulation with a cessation of acute symptoms. Relapses are, however, much more frequent than after the use of quinin.

Tartar emetic, intravenously, has been tried thoroughly and found wanting.

In the other forms of malaria, that is, quartan and estivo-autumnal, methylene-blue is probably the best substitute, though so far inferior to quinin as to be regarded as a makeshift. Only the purest preparation should be employed, otherwise headache, nausea, vomiting, diarrhea, strangury, and albuminuria may ensue. The dose is from 1½ to 3 gr. given every three hours until from 7½ to 15 gr. have been given in twenty-four hours. The patient should always be forewarned of the blue color imparted to the urine and feces.

When all other measures fail the patient may be advised to visit a spa of radio-active waters, of which there are several in this country.

BLACKWATER FEVER

It is unnecessary to review the history of the discussions or to rehearse the arguments for or against the etiologic relation of quinin to blackwater fever. No valid conclusion can be reached except through results of a large series of cases treated with and without quinin. Such a series, collected by me from the literature several years ago, shows that in 2,107 cases treated with quinin there were 538 deaths, a mortality of 25.5 per cent, and that among 1,183 cases treated without quinin there were 123 deaths, a mortality of 10.4 per cent. While the results of the series prove that the mortality is higher under the routine treatment with quinin, they should not be taken to exclude absolutely the use of quinin in some cases of blackwater fever, for under certain circumstances quinin may be of value. In my opinion the only conditions in which quinin is indicated are: (1) where the parasites show no tendency to disappear after forty-eight hours from onset; (2) in the infrequent cases of intermittent hemoglobinuria where the outbreak corresponds with parasitic sporulation.

If it is decided to give quinin it should be injected intravenously. Given by mouth it upsets the stomach and may not be absorbed.

Even in cases of mildest onset the patient should be confined to bed from the start and should be kept quiet, either by suasion or by sedatives. Sudden death on slight exertion sometimes occurs, anuria and heart failure being the chief dangers. Chilling of the body, especially when the temperature is low, should be carefully avoided. When vomiting is not a prominent symptom, liquid nourishment may be given freely; buttermilk and albumin water are the most suitable substances. Sweet milk is often ejected as a thick curd, molded ropy by the esophagus in the act of vomiting. Animal broths, barley and oatmeal water, lemonade and orange juice are allowed. Rectal alimentation is unsatisfactory.

The bowels should be moved early and often and calomel possesses advantages over other purgatives; it is more easily retained, is a bland diuretic and is the best of intestinal antiseptics. Too large doses are usually advised; 3 to 5 gr. are, as a rule, sufficient, repeated if necessary.

The fever does not usually run sufficiently high to call for treatment. The coal-tar preparations should be assiduously avoided. Cold baths may be productive of harm by increasing the blood destruction, but in hyperpyrexial cases sponging with tepid water may be resorted to.

Vomiting, if not intense, is often benefited by a mustard plaster on the epigastrium. Draughts of hot water or of carbonated water sometimes assist in relieving this troublesome symptom. Cracked ice may be tried. Morphin hypodermically should be given unhesitatingly when other measures fail; any evil effects are more than out-weighed by its enabling the stomach to retain liquids.

Probably the most important indication in the treatment is the prevention of suppression. Medicinal diuretics usually do harm, though theobromin sodium salicylate may be given in an emergency. Water is the best diuretic and as much should be given by mouth as will be retained. Salt solution by hypodermoclysis or intravenously is a valuable means of combating and treating anuria. In mild cases where the urine is free the rectal use may be sufficient.

Supportive measures are essential. Alcohol in all its forms is inadmissible. Digitalis has proved serviceable and the aromatic spirits of ammonia is of value. Transfusion of blood has been used, it is said, with excellent results.

The after treatment should have a care for the diet, which should be non-nitrogenous and consist largely of liquids at first. A tonic of organic iron is indicated, and digestive disorders when present should receive appropriate treatment.

A question of practical importance is how soon after the attack to begin the administration of quinin. A dose given too early may possibly, in some persons, precipitate hemolysis. On the other hand, delay may permit an outbreak of malaria accompanied by hemoglobinuria. I am of the opinion that quinin should be begun, carefully at first, a short time after the attack has subsided and before blood regeneration is fairly established. One grain of quinin three times daily, increased gradually every other day, is a safe procedure. If the temperature rises or the urine becomes distinctly darker no further attempt to increase the dose should be made.

PREVENTIVE MEASURES

Preventive measures in malaria are accompanied by the most brilliant results when systematically applied.

Prophylactic measures may be directed toward the destruction of the malaria parasites within the body of man, the destruction of the mosquitoes which are capable of transmitting the parasites, and the prevention of mosquitoes gaining access to man. The parasite may be opposed either in man or in the mosquito. The mosquito may be combated either in its aquatic or in its aërial stage. Prophylaxis may be conducted by a community or by an individual, may be public or private, offensive or defensive.

As is well known, malaria is now almost or entirely absent from regions in which it was formerly prevalent, and in other places is rapidly diminishing. In the regions in mind the change was independent of designed efforts for the eradication of the disease; in fact, it occurred in most instances before the discovery of either the malaria parasite or of the rôle of the mosquito in the dissemination of the disease, and was an unexpected result of the progress of civilization.

The most brilliant results in the prophylaxis of malaria were those obtained by Gorgas in Panama, one of the most insalubrious regions upon the face of the earth, having been called during French occupation "the Frenchman's grave." It is a common report that in the railroad between Panama and Colon every crosstie represents the corpse of a laborer.

The canal zone is fifty miles in length, with Panama and Colon at each end. The average number of employees was 40,000. The efforts consisted in the destruction of breeding places only within two hundred yards of the camps and villages, no attempts being made to deal with those farther off. All the houses were screened and the people urged to use mosquito bars. Quinin was furnished them and they were advised to take 3 gr. daily. The abolition of the breeding pools was regarded as a most important measure. Owing to the heavy rainfall and the luxuriant vegetation the ditches filled rapidly with grass, and it was found much cheaper to concrete them. Subsoiling by means of the tile drain covered with rock and soil was used wherever possible. The result is that the death-rate has been lowered until it does not exceed that of New York City.

Destruction of breeding pools for the anopheles is an efficient preventive measure. It is chiefly through the eradication of breeding places that so-called unconscious prophylaxis has accomplished its results. This method has received the chief consideration in the greatest antimalarial campaigns. It is more permanent and possesses the further advantage in many instances of being cheaper in the end.

It is neither necessary nor in every case advisable to remove the surface water from the whole of a malarial country, but only in the inhabited regions or where anopheles are known to breed. In the Panama campaign the area of destruction extended only two hundred yards from camps and habitations. This should probably be the minimum radius, though work at a much greater distance is only a useless expense.

In the area to be protected the land should be cleared of weeds, undergrowth, bushes, and unnecessary trees to promote evaporation and prevent the formation of puddles. Grocery cans, broken bottles, buckets, and old tinware which might retain water should be buried. Water barrels, tanks, cisterns, and wells should be emptied, filled, or screened. Gutters should be maintained in such a condition that water cannot accumulate.

The stock pond, so common in the vicinity of habitations in some sections, is a menace to both man and beast and should not be tolerated.

The care of streams and large bodies of water is ordinarily simple, since these rarely threaten sanitation as anopheles breeders. Within the protected area the banks should be cleared of dense weeds and bushes, eddies prevented where possible, and pools along the edges drained into the channel.

In the case of streams that get very low after the rainy season, leaving a chain of pools along the river bed, these pools should be drained into each other and an attempt made to reëstablish a flow and to permit of scouring and the access of fish from the larger pools. Where the pools are small much water can be gotten rid of by the use of brooms.

In the case of large bodies of water subject to overflow, the problem is more difficult. The primary effect of the submerging of land, while the water is high, is to diminish malaria. The secondary effect, after the waters have receded, is to cause a marked increase. The effect upon malaria of inundations is almost yearly observed in the valleys of the Nile, of the Mississippi, and of other large streams. Levees, dikes, and other engineering means of large dimensions are the only remedies; these, being expensive, are rarely employed merely for sanitary purposes.

Marshes and swamps when too extensive to be filled may be effectively drained. The drains should be narrow, of sufficient depth and fall to drain effectively, and may be parallel, crowfoot fashion or otherwise, as best suited to local conditions. If concreted they require less after treatment and may be cheaper in the end. If not concreted they should be frequently inspected to prevent caving, deposit, or filling with vegetation. The tile drains are usually very efficient.

Large swamps in the vicinity of streams have been rendered unfit as breeding places by directing the course of the stream through them. The water is thus given a current and, if the stream contains much mud in suspension, the bed of the marsh is gradually filled.

Fresh-water ponds close to the sea have been successfully treated by filling with salt water. Water strong in salt is not attractive for breeding purposes, though brackish water may harbor numerous larvæ.

The rendering innocuous of borrow pits along railroad lines is difficult. It is much easier to prevent the stagnation of water during the construction of the road than it is to remedy the defect after completion. Filling and drainage are the best correctives.

The destruction of smaller pools and puddles is usually simple and goes far toward prophylaxis, since it is in such places that anopheline mosquitoes breed by preference. Filling is by far the most permanent, hence the cheapest and most desirable method by which to deal with these collections of water. Pools in ditches along the sides of roads, wheel ruts, hoof prints of stock in soft ground, water remaining in natural inequalities in the ground and in excavations for various purposes should be assiduously attended. The work should be conducted by one who is familiar with the rudimentary principles of drainage.

There are circumstances under which it is impossible to destroy the breeding pools. Here the use of petroleum is indicated. This oil is also useful in antimalarial campaigns as a temporary measure in part of the work while permanent means are being employed elsewhere.

An oil should be chosen which spreads rapidly and evaporates slowly. The refined illuminating oil evaporates readily, hence is too expensive for work on a large scale. The most suitable is the fuel oil or blast-furnace oil. The oil, forming a film upon the entire surface of the water, chokes the air tubes of the larvæ which come to the surface to breathe. The pupæ expire even earlier than the larvæ, since they require more air. Furthermore, not a few adult female mosquitoes in the act of oviposition are thereby destroyed.

The pool should be cleared, as far as possible, from weeds and algæ which interfere with the spread of the oil. The oil should be poured from a watering pot, sprayed by means of a force pump, or painted over the surface with saturated cloths tied to the ends of sticks. An automatic oiler may be improvised by placing a barrel of oil a few feet above the water, to give the oil the necessary spread, and having a perforation in the bottom of the barrel to drop about twenty times to the minute.

The quantity of oil which has been found amply sufficient is 1 ounce for each 15 square feet of surface. It has been estimated that a barrel of oil costing only a few dollars is sufficient to cover 96,000 square feet of surface.

Evaporation, rains, and winds prevent permanent results, so that the oiling must be repeated. Intervals of two or three weeks are the proper average, and certain days of the month should be systematically chosen. It is best to begin the oiling in the spring to prevent the first generation.

Where it is not feasible either to drain or oil a breeding pool, the introduction of small fish has been practiced with success. Certain species of fish prey upon the eggs, larvæ, and pupæ of mosquitoes, and even upon adults when about to emerge from the pupal shell or when in the act of oviposition. The common top minnows (Gambusia and Fundulus) and the sunfish are excellent for this purpose. The former being very voracious and top feeders are especially adapted for the destruction of anopheles larvæ. They are fast breeders and resist the drying of pools in a remarkable degree. Sticklebacks, goldfish, and roach are also larvivorous. It is doubtful whether the common German carp, on account of its feeding habits, is of any use for this purpose. The tadpole is valueless for the destruction of larvæ. Ducks destroy many larvæ. The larvæ of the dragon fly, the water boatman and the hairworm devour mosquito larvæ.

The natural enemies of adult mosquitoes are few and practically insignificant. Dragon flies, nighthawks, whippoorwills, swallows, bats, and certain species of lizards destroy a number and some are killed by parasitic mites and small suctorial flies.

An ideal prophylaxis destroys the breeding pools or the aquatic stages of mosquitoes, but remedies against the adult insects are sometimes necessary. For this purpose a great variety of substances has been tried. One of the most primitive of measures is the smoldering fire of chips, rags, and feathers, to be seen in summer twilight to the windward of nearly every negro cabin.

The most practical means are the fumes of burning sulphur and of pyrethrum powder. The room to be fumigated should be made as nearly airtight as possible.

Efforts to destroy the malaria parasites in the human body assume two modes. The first consists of the radical cure of the malaria-infected individual, the prevention of a relapse, thereby benefiting the individual and annihilating a source of danger to the community. The second mode consists of the administration, to persons not necessarily infected, of a drug which destroys the parasite soon after the latter is introduced into the body, before the incubative stage is completed.

Cases of latent and atypical malaria are of greater importance to prophylaxis, being sources of greater danger to communities than are typical acute cases. The duration of the acute atttack is short; the patient is apt to be placed under relatively favorable conditions and to receive quinin; he does not wander and disseminate the disease; and his blood may contain but few sexual forms of the parasite. On the other hand, the subject of latent malaria may harbor parasites for months and, the condition being unrecognized or ignored, he does not take quinin, and is a fountain of infection in diverse places and for prolonged periods.

Theoretically the administration of quinin to healthy individuals for the prevention of malaria is not an ideal method of prophylaxis, for, strictly speaking, it does not prevent infection, but destroys the parasites in the incubative stage after inoculation into the human body. But no one method satisfies all conditions; each has its advantages and its limitations, and frequently two or more methods must be employed simultaneously.

Quinin prophylaxis is indicated in proportion to the difficulty of pursuing more permanent methods. It is valuable where screens and bars are not available, as in camping, marching, traveling, or where the occupation takes one out at night. When residents of non-malarial countries go into malarial localities, especially in the rural districts, for short spaces of time, quinin is a most valuable prophylactic. After infection is known to have occurred, quinin is, of course, essential not only as a cure, but as a preventive. It may be employed effectively where it is impossible to destroy the mosquitoes or as an adjunct to other measures.

One objection, varying considerably with individuals, is cinchonism, which may even amount to very unpleasant nervous or gastric disturbances.

To be efficient as a preventive of malaria quinin must be taken in sufficient dose during the entire malarial season. It is difficult to make ignorant people realize the importance of taking treatment during several months to prevent, maybe, merely a chill, and few governments have the authority to force them to do so. No permanent results are to be obtained in this way unless all take drug throughout the malarial season and all cases of malaria are radically cured.

The expense of public prophylaxis with quinin on a large scale is enormous, in fact, in some instances prohibitory. Money spent for quinin to be given in inadequate doses at irregular intervals is wasted.

The size of the dose and the interval at which the prophylactic is administered are of the utmost importance. Very varying quantities have been employed at different intervals, but the established methods have about settled down to that described below.

The method canonized by Koch consists in giving 1 gm. of quinin every sixth and seventh days, seventh and eighth, eighth and ninth, or ninth and tenth days, according to the danger of infection. This manifestly leaves several intervening days in which there is no quinin in the circulation. In localities, therefore, in which estivo-autumnal malaria is prevalent, the shorter interval of administration should be preferred on account of the shorter period of incubation of this form of malaria.

The prophylactic value of excluding mosquitoes is in proportion to the number of anopheles and the proximity of infected persons.

A properly protected house should have every door and window screened. In some localities it is advisable to cover even the chimneys with wire netting. Doors should be provided with springs to necessitate closure. Where mosquitoes are plentiful and a door is much used, a double door, with an intervening vestibule after the manner of the Italians is to be preferred. A screened porch permits of sitting in the air in the evening when it would be dangerous to do so otherwise.

The selection of the gauze for screens is of the highest importance. The mesh of the wire netting often used, No. 12, is too large, permitting small mosquitoes to pass. None should be used with fewer meshes than eighteen to the inch. In the absence of wire gauze, cotton mosquito netting may be employed, but, being frail, soon becomes torn and useless.

Persons whose occupations keep them out at night in highly malarial places, such as watchmen and others, should be protected with veils and with leather gloves having gauntlets.

The mosquito bar is indispensable in malarial countries. Besides being very effective when properly adjusted, it is the most inexpensive of all prophylactic methods.

As with every other method for the prevention of malaria, screens have certain shortcomings. It is evident that if malaria is to be eradicated by these means from a locality, every house should be screened, otherwise only those in the protected houses would be exempt, and only so long as they remained in such houses. It is out of the question both on account of the expense and because of the poor construction of many of them, permitting mosquitoes to enter through crevices and other openings. The fact that screens offer a slight hindrance to the free circulation of air in hot countries is of little moment in the face of the benefits derived from their use, and they must be considered as one of the most effective means of private prophylaxis.

Of local applications to drive away mosquitoes, many substances have been tried, particularly the essential oils, of which the oils of citronella, eucalyptus and lavender are probably the most efficacious. Petroleum, infusion of quassia, naphthalene, powdered sulphur, camphor, garlic, the oils of cloves, tar, pennyroyal, chrysanthemum, and anise have been employed with varying degrees of success.

In India the punkah is employed to keep the air in motion, and for this reason is found to be of service in driving away mosquitoes. The electric fan has this effect also, but for obvious reasons should not be employed for this purpose during sleep.

Isolation of the malarial patient is as truly indicated as in yellow fever, both diseases being conveyed in the same manner. Mosquitoes must become infected before they can infect man; breaking the vicious circle at this point would extirpate malaria. Isolation is demanded not only for the good of the community, but to prevent reinfection of the patient, who should be confined under a well-adjusted bar until a radical cure is effected. It is not to be expected, however, that as much can be accomplished from the isolation of malaria as from the isolation of yellow fever. Many cases of malaria entirely escape medical treatment, and a malarial subject may be a source of infection for a year or more, while yellow fever is infectious for only a few days.

Since it has become evident that so great a proportion of the inhabitants, especially the children of tropic countries, harbor malaria parasites in the blood, segregation of the whites from the natives has been proposed and in some instances practiced with success. While the question is of some import in this country, the negro quarters in most of our towns are fairly well defined from those of the white. Upon the premises the householder should see that his servants' quarters are as thoroughly screened as his own. In the choice of camp sites native houses should be avoided beyond the limit of flight of mosquitoes if possible.

Great good is being accomplished in the prophylaxis of tuberculosis by education, keeping the main facts in the etiology and prevention constantly before the eyes of the people. So much cannot be expected from malaria on account of the ignorance and carelessness of the class and race of people most scourged, but undoubtedly some good may accrue from this method. The Europeans, at home and in their colonies, have obtained some results in the prophylaxis of malaria by teaching the people the elements of the cause and prevention of the disease. Lectures, illustrated by stereopticon views, are held publicly. Publications in simple language, in the form of circulars and tracts, and even appropriately illustrated post cards are scattered broadcast. The Italian Society for the Study of Malaria has distributed about two million of these circulars. The principles of prophylaxis are instilled into the minds of the school children and made attractive and impressed by means of illustrated charts. The lay press has been used to advantage. With such means the formation of an antimalarial league can do much for a community.

To be thorough, malaria prophylaxis should be handled by the government. Destruction of the breeding places of the mosquitoes, which is by far the most radical method, is, in many instances, too expensive to be done by individuals. The formation of drainage districts, the expenses of which are paid by those benefited, is an effective plan, and so enhances the value of real estate, from both agricultural and sanitary standpoints, that there should be no opposition.

It should be the duty of the authorities of every malarial country to remove the duty from quinin and to maintain a high standard of purity and a low price.

Private prophylaxis consists of measures having reference to the person and to the premises. Personal prophylaxis is synonymous with proper hygiene. Suitable food, water, and clothing are essential. Regular hours must be kept, and constipation, chilling of the body, and excess of all kinds must be avoided. Prophylactic quinin is not constantly necessary for residents if the premises are in proper condition, but is suitable for strangers and under conditions where mosquitoes cannot be excluded. Persons sleeping upstairs are less liable to infection than those upon the first floor.

Pools are to be filled, drained, or oiled, and vessels emptied. It has been suggested that a tub of water be kept on the place to tempt mosquitoes to breed, and that this be emptied every few days. Stock ponds should be drained, oiled, or stocked with fish. The houses should be thoroughly screened and, where these are not effective, or if infection occurs, bars must be employed.

CHAPTER XXX

AMEBIC DYSENTERY (INTESTINAL AMEBIASIS)

RICHARD P. STRONG

Although amebic dysentery or intestinal amebiasis is a very common disease throughout tropical and subtropical countries, it also occurs sporadically in most countries in the temperate zone. Cases of the disease are not very uncommon in the northern United States, in Great Britain, France, and other countries of northern Europe, and in a number of these instances the individuals infected have not been outside of these localities. Therefore the physician in most parts of the world may be called upon to treat cases of this affection. The disease, which is dependent upon infection of the large intestine with pathogenic amebæ, is characterized clinically by a variable mode of onset and a course of great irregularity. In only those cases where the infection is severe, or where there are other contributing causes, does amebic dysentery with mucus, and blood, and motile amebæ in the dejecta result. In other cases of infection there may be intermittent attacks of diarrhea, of constipation, or abdominal pain, or the patient may have no symptoms at all attributable to the amebæ. Nevertheless, in some of these cases with no intestinal symptoms the infection may continue and extend; the amebæ may penetrate the mucosa and enter the veins of the submucosa and grave complications such as liver abscess may result. On the other hand, many individuals serve as the host for apparently the same species of amebæ pathogenic for other human beings, and discharge the cysts of these organisms in their feces for over long periods of time without ever having suffered with any apparent inconvenience from them.

PROPHYLAXIS

In connection with the prophylaxis of amebic dysentery, it is of importance to consider the source of the infection in this disease which occurs naturally through the medium of drinking water or food contaminated directly or indirectly with infected fecal material. Infection of man frequently follows upon the ingestion of the living amebic cysts which, after being swallowed by the individual, liberate the contained amebæ in the intestine, probably under the influence of the ferments contained therein. These cysts are formed normally in the intestine of the host who is a carrier of the infection, and are passed in his dejecta. Hence any vehicle of these cysts in a living condition to the mouth and alimentary tract of man is of importance in relation to prophylaxis. The cysts, upon being passed in the dejecta, must find some suitable environment in order to remain viable. Since they are killed by complete desiccation, dust is probably not a source of infection. However, in a suitable liquid or damp medium they may remain alive for a considerable period. Thus, they have been shown to survive for at least two to three weeks in water, and sometimes for the same period in moist feces, particularly if they are kept cool. It has also been demonstrated that flies, such as Musca domestica, Fannia canicularis, as well as Lucilia, and Calliphora, which have fed on infected feces, will ingest the cysts and later deposit them unaltered in their excreta. Buxton found cysts of Entameba histolytica in 0.3 per cent of the house flies caught in Mesopotamia. According to other experiments, the cysts may appear in the excreta of the fly as early as five minutes and as late as twenty hours after feeding; in exceptional instances for as late as forty-two hours, if the fly is not fed in the interval. A single house fly may take up 1 mg. of feces in one-half hour. If the cysts in the fly droppings are deposited upon a moist medium, such as certain varieties of food, flies obviously constitute another means of carrying the infection.

It has been pointed out that the cysts are formed normally in the intestine of man, who constitutes the carrier of them. Such an individual may never have suffered from any disturbance due to this infection, or on the other hand he may be a patient who has partially or wholly recovered from amebic enteritis or dysentery. We do not know exactly what condition in the intestine causes the amebæ to sometimes encyst, but we suppose that they do so under certain conditions which are unfavorable for the vegetative stages of their growth. While man usually becomes infected by swallowing the cysts of amebæ, it is by no means certain that he may not sometimes become infected from swallowing in large numbers the vegetative forms which have passed under certain conditions unchanged through the stomach into the intestine. In fact, Walker has produced amebic infection in 2 men by feeding them portions of the stool of a man suffering with an acute attack of amebic dysentery containing motile Entameba histolytica. In view of these facts it would be dangerous to assume, as has been done by one author recently, that the sufferer from acute amebic dysentery is unable to transmit his infection to other individuals and does not constitute a source of infection. Some years ago the writer called attention to the danger of the spread of amebic infection in the tropics by monkeys whose dejecta contain entameba, and who sometimes suffer with amebic dysentery. These animals may pollute local water supplies, particularly where rain water is used for drinking purposes and stored in uncovered receptacles. While sporadic cases of entamebic dysentery have been reported in dogs, and cats may be artificially infected with Entameba histolytica, it is not probable that these animals play an important part in the spread of the human infection. Lynch has found wild rats in Charleston, South Carolina, affected with amebic ulcerative colitis, and has produced this disease in rats by feeding them human feces containing amebæ, both in the active and resting stage. He believes the organism in the rat to be Entameba histolytica, and suggests that amebic dysentery may be sometimes caused in man by the ingestion of food soiled with the excrement of such infected rats. Wenyon states that he knows of no method of distinguishing the amebæ of the rat from Entameba coli of man, but he does not explain the ulcerative amebic dysentery produced in the rat.

In the Philippine Islands it has been noticed that sometimes a heavy rainfall will increase markedly the number of cases of amebic dysentery in a district. Such increase of the infection is probably caused sometimes from the surface infection of wells and water supplies, by the washing out of cesspools and other places contaminated with human fecal material. In Egypt it has been observed that there is an increase of the disease at the time of the annual overflow of the Nile, which probably results from a similar cause. While the amebæ that are found almost constantly in the water supplies in some tropical countries are usually of the free living type, and apparently non-pathogenic for man, it is still premature to conclude that such waters which contain vegetative forms of amebæ in large numbers are pure, and such water supplies should, in view of our present knowledge, be regarded as unsafe for drinking purposes unless sterilized. For we have not the evidence to show that some of these amebæ may not under certain conditions be or become pathogenic for man. The recent investigations of Gauducheau are in accord with this view.

In certain countries of the Far East, human excrement is used for fertilization of the fields, and this may constitute another means of spreading the infection.

From this discussion it is obvious that prophylaxis, particularly in those regions where the disease is prevalent, must consist in the avoidance of all unsterilized drinking water that may possibly be contaminated with human feces. Other important protective measures are the avoidance of eating uncooked fruits and vegetables particularly liable to contamination, such as lettuce, celery, and other salads; the protection of food from contamination with fly droppings by screening, etc., and the destruction of flies. Particular attention should be paid by the physician to the treatment of diarrhea or any intestinal disturbance which may possibly bring about a more favorable condition in the intestine of the patient, for the propagation of amebæ which might have been introduced later or have been present at the time. In the present state of our knowledge we cannot say with certainty that amebæ may penetrate the perfectly normal mucous membrane of the intestine, and it may be that slight abrasions of the intestinal wall must first be produced before such penetration and amebic ulcerations of the intestinal wall occur. It has not been demonstrated that the amebæ causing amebic dysentery in man produce a proteolytic ferment capable of dissolving the intestinal epithelium, although some years ago Mouton reported the presence of a proteolytic ferment resembling trypsin from cultures of free living amebæ isolated from garden earth and grown in symbiosis with the colon bacillus.

Prophylaxis should also include the disinfection of stools of cases of amebic dysentery as well as those of carriers. Wenyon and O'Connor found that cresol killed all cysts immediately, in a strength of 1 to 20, in one minute in a strength of 1 to 30, in one-half hour in a strength of 1 to 100, and not at all in dilutions of 1 to 2,000. Cresol, therefore, can obviously be employed for the disinfection of dysenteric stools or for the hands of those who have to care for patients. Acid sodium sulphate tablets and chlorinated lime tablets used for the purification of water according to their experiments failed to kill the cysts of amebæ. Hence the boiling of drinking water or the use of distilled water in districts where the disease prevails widely is recommended.

Obviously public prophylaxis consists mainly in the improvement of the general sanitation of a district in the proper and safe disposal of human excrement and the provision of a safe water supply. It appears doubtful if there is any acquired immunity against amebic dysentery and no methods of immunization against infection with amebæ have been described. Moreover, no one has demonstrated that amebicidal or other substances giving rise to an active immunity are produced in the course of amebic dysentery. In view of the fact that, in the examination of large series of apparently perfectly well individuals in a number of countries in the temperate zone where amebic dysentery does not prevail to any appreciable extent, at least 3 per cent have been said to be infected with the cysts of Entameba histolytica; and since there is no simple, efficient and sure method of ridding individuals of these cysts, general treatment of such carriers, with the object of destroying the amebæ and cysts in the intestine, is not recommended. Also for obvious reasons the detection and isolation of all healthy carriers who are passing cysts is not recommended as a prophylactic measure.

Treatment of Ameba Carriers.—Attention has already been called to the presence of cysts of Entameba histolytica in the feces of healthy individuals. Stiles found that, in the microscopical examination of 13,043 fecal specimens from 8,029 persons in 48 institutions located in 23 states, 4.1 were infected with cysts of Entameba histolytica. In a country where proper disposal of human feces is carried out, the individual who harbors cysts of Entameba histolytica in the intestine cannot be regarded as a menace to man. Hence his treatment from the standpoint of public prophylaxis is not justifiable. Moreover, such infections have been known to exist over long periods of time without the slightest symptoms, and individuals who have been known to be carriers during life and have succumbed to other diseases have shown no lesions of the intestine visible to the naked eye at autopsy. Carriers of Entameba histolytica have been divided into two classes termed "contact carriers" and "convalescent carriers." The former have been defined as individuals who have never suffered from amebic dysentery or intestinal disturbances, and the latter those who have recovered from amebic dysentery or enteritis without loss of infection. It is often difficult to rid the individual of the cysts of Entameba histolytica by any known treatment. The various methods which have been particularly employed are described in detail later in this article. In large series of cases of amebic infection, some are always found to be refractory to treatment. Shall the physician persist in the eradicative treatment of contact carriers of amebic infection? At least in countries where amebic dysentery does not prevail, it would seem to be more advisable to continue to observe such patients at intervals rather than to submit them to frequent recurrent medical treatment; and even in some countries where the disease occurs more commonly, this would seem to be the wisest course to pursue. Very recently Le Noir and de Fossey have suggested rendering the intestinal conditions temporarily more favorable to entameba by the administration of bile, which may be given in the form of dried bile or bile extract preparations. Usually 9 capsules a day are given, each containing 0.2 gm. of bile extract, 3 at each meal. This dosage is increased by 3 capsules each day until diarrhea results and the stools contain numerous living amebæ as well as cysts. These authors suggest that eliminative treatment should then be begun promptly as the young amebæ are less resistant than the cystic forms. The writer believes that a more conservative or expectant attitude should prevail in regard to the persistent treatment of contact carriers who are passing only cysts of Entameba histolytica and not vegetative forms.

Treatment of Individuals Harboring Vegetative or Propagative Forms of Amebæ.—Formerly it was often assumed by the physician or he was informed by his laboratory diagnostician with reference to an individual who continued to pass vegetative forms of motile amebæ in the stools for long periods of time, without symptoms of any disease, that the individual was infected with a harmless ameba of man, Entameba coli. More recently we have come to realize that Entameba histolytica may also sometimes live for long periods of time in the intestine of man without producing unfavorable symptoms to the host. Walker fed 20 volunteers with Entameba histolytica, either in the encysted or motile stage. Although 17 of these individuals became parasitized, only 4 of the 18 men developed dysentery, the symptoms first appearing only after a long and variable time following the ingestion of amebæ and their appearance in the stools. Thus while the amebæ appeared in the stools in the 17 individuals, usually within from four to six days after feeding, the interval before the symptoms of the dysentery which developed in only 4 was nine, fifty-six, seventy-seven, and ninety-four days, respectively. Recently the statement has been made that, in all individuals infected with Entameba histolytica, the amebæ in order to live and multiply must continually consume the lining of the colon, and that there can be no doubt that the carrier of Entameba histolytica, though he displays no symptoms, always has a more or less eroded or ulcerated gut. Such an assumption is entirely unwarranted since there is no definite evidence to support it. On the other hand, as those who have had wide clinical and postmortem experience with amebic infection in tropical countries realize, amebic ulcerations of the intestines may sometimes exist without producing any unfavorable intestinal symptoms.

If it were always practicable for the physician to receive from the protozoölogist or the laboratory diagnostician correct information regarding the occurrence of a pathogenic or non-pathogenic ameba of man in the stools of a given patient, his procedure in regard to treatment would often be much simplified. However, with our present knowledge regarding amebæ, we sometimes are not able to say with certainty whether a motile ameba in the stools is pathogenic or non-pathogenic under certain conditions for man. Sometimes the clinician, from his observation of the symptoms of the patient over a long period of time, is really more capable of answering this question than is the laboratory worker from the microscopical examination of the ameba alone. To-day protozoölogists differ considerably among themselves concerning the number and the differentiation of the intestinal amebæ in man and even in relation to the specific diagnosis of the different species. During the past few years the following species of human intestinal amebæ have been particularly described and studied: Entameba histolytica, Entameba coli, Endolimax nana, Pseudolimax or Iodameba butschlii, Diendameba fragilis, Councilmania lafleuri, Entameba phagocytoides and Entameba paradysenteria. For the zoölogical description and differentiation of these species, the reader must obviously consult other articles which consider particularly the subject of diagnosis in amebiasis, as lack of space prevents their consideration here. Of these species Entameba histolytica is generally recognized to be pathogenic for man. Gauducheau believes that Entameba phagocytoides is also pathogenic though it is a cultivable species. No satisfactory experiments have been performed with the remaining species, with the exception of Entameba coli, which demonstrate their pathogenicity or non-pathogenicity, although they have been observed in individuals with no symptoms of intestinal disease. A few observers still incline to the belief that all amebæ found in the intestine are or may become pathogenic. We know nothing yet as to whether the pathogenesis of some species of amebæ under certain conditions may be increased, and it must be admitted that the whole subject of the classification and means of distinguishing the species of pathogenic and non-pathogenic amebæ is still in a very unsatisfactory state. While the differentiation of species of amebæ in the human intestine has become of great interest to the specialist, it has not been of exceedingly great benefit to the clinician. This is particularly so because, while there are very few specialists who are sufficiently familiar with the morphological details to distinguish the various different species of motile amebæ which have been described in the intestine of man, only plausible guesses may sometimes be made with reference to the clinical significance of the parasite, unless the condition of the stool is taken into account and the presence or absence of blood, mucus, intestinal epithelium, leukocytes or other cells, and Charcot-Leyden crystals are taken into consideration. A single example of the difficult situation regarding the differentiation of species will suffice. During 1921, Kofoid and Swezy, who have for some years devoted particular attention to the study of amebæ, have described and figured in detail the free, encysted, and budding stages of a new ameba, Councilmania lafleuri, as a parasitic ameba of the human intestine which Wenyon in January, 1922, insists is no other than Ameba coli. Rodenhuis has recently found no less than 29 cysts of Entameba histolytica containing 8 nuclei apiece, and 1 containing 12 nuclei, instead of the supposedly maximum number of 4 as previously described. Other observers have also encountered 8 nucleate cysts of Entameba histolytica, which further complicates the differentiation of this species from Entameba coli with its 8 nucleate cysts.

If the clinician finds motile amebæ in stools which also contain blood and mucus, and particularly if the amebæ contain red blood-corpuscles, he is justified in immediately instituting treatment against the parasite. If, on the other hand, the patient has never had any intestinal disturbance or symptoms that may be referred to the intestine, and the stool which has been freshly passed appears normal in every way with the exception of the presence of a few amebæ which answer to the description of Entameba coli type, it would seem advisable that the patient be kept under close observation with occasional examination of the stools and an expectant plan of treatment.

In some patients with chronic relapsing amebiasis it may be extremely difficult to find amebæ after the most prolonged and careful search. In such instances the question of treatment is especially important as other relapsing conditions such as sprue have to be considered. It may sometimes be possible to reach a decision by using a Kelly sigmoidoscope which may reveal characteristic ulcerations.

TREATMENT

General, Dietetic, and Symptomatic Treatment

Patients with acute symptoms of dysentery should be confined to bed. In the most severe forms, when very frequent stools containing much blood and mucus are being passed, the diet should consist of nothing but rice, barley, or albumin water. As the condition improves, milk may be added. Rest for the inflamed intestine is desirable and, in order to secure this, hypodermic injections of morphin sulphate, gr. ¼ (gm. 0.016) with atropin may be given every three or four hours. At this stage of the disease the emetin treatment, providing of course that the amebæ have been found, should be begun. The details of this treatment are given later in the article. Local treatment, however, is contra-indicated during the period that the acute dysenteric symptoms are present. It is very important to secure rest for the patient and for the acutely inflamed colon. If this can be accomplished and the peristalsis quieted, the condition usually improves, at least temporarily. As the acute dysenteric symptoms begin to ameliorate, Dover's powder, gr. 10 (gm. 0.6) may be substituted for the morphia. This may be continued until the acute symptoms have subsided. As long as any intestinal irritation exists, the diet should be restricted. Fresh milk, when obtainable, should be chiefly employed. If curds appear in the stools, it is advisable to add limewater or to peptonize it. Other liquid nourishment, such as beef or chicken broth, may be substituted if milk is not well borne. It is advisable to feed the patient frequently and in small amounts. As the unfavorable intestinal symptoms subside, other liquids and soft food may be gradually added to the diet. Not until the stools appear perfectly normal should general diet be permitted. Any lesions of the large intestine will be more advantageously affected by liquid than by solid food. If the patient is seen before the symptoms are very acute, a saline purge may be given, but, if the severe dysenteric symptoms have begun, such treatment is contra-indicated. In very mild attacks, or when the disease has become subacute or chronic, and the intestinal symptoms are not severe, it appears sometimes more advisable not to confine the patient entirely to bed, since his strength will be better retained when he is allowed to sit up and be outdoors in proper weather. During any acute relapses of the diarrhea or dysentery, he should be confined to bed. In the advanced cases, should anemia occur, some iron preparation is advisable, and, when there is lassitude and anorexia, a course of strychnia with cardamom compound is often of some value. Patients in whom the infection has become chronic and who are residing in a tropical country are often benefited by a change to a cooler climate.

SPECIFIC TREATMENT

For the eradication of the amebæ, the best results have been obtained from the use of emetin, an alkaloid of ipecacuanha, or ipecac, the hydrochlorid of which has the following formula: $C_{29}H_{40}O_4N_22HCl$. It is particularly from the studies of Vedder, and their application by Rogers, and others, that this progress in the treatment of the disease has largely been made. Ipecac is contained in the dried root of a Brazilian herb, Psychotria or Cephaëlis ipecacuanha, a rubiaceous plant. It was said to have been in common use in parts of South America long before it was brought to Europe by Piso about 1650. It was also supposed to have been one of the ingredients of a formula for the treatment of dysentery with which Helvetius, at the request of Louis XIV, successfully treated the Dauphin who was suffering with this disease. The formula for the preparation at the time was secret and, after its success had been demonstrated in this way, it was purchased by the French Government for 1,000 louis. Since this time ipecac has been used as a remedy for dysentery in various parts of the world. It has been shown to be particularly effective in the treatment of amebic dysentery, but it also often has a favorable action in other forms of dysentery. This is perhaps in part due to the fact that the drug exerts a powerful local constricting effect upon the blood-vessels, and that it tends to arrest and control hemorrhages from the intestine as well as from the lungs, as Flandin, Renon, Chauffard, and others have recently demonstrated.

Ipecac was used in the treatment of dysentery by many physicians in India during the nineteenth century, and in 1858 Docker in Mauritius reported many cures from the use of the powdered root in 60-gr. doses. During our Civil War its use was particularly advocated by Woodhull and Forwood. Woodhull later advised its use in the Philippine Islands. In Great Britain the late Sir Patrick Manson for many years advised its employment in all forms of dysentery. Partially, no doubt, on account of the emesis which the drug generally produces when given by mouth, it never became a popular remedy. Its use was also undoubtedly influenced by the fact that it does not prove as effective in treating other forms of dysentery as it does the amebic one. The unfortunate mistake was also made of recommending the use of a preparation *ipecacuanha sine emetina,* which produced no emesis, but from which the most active alkaloid in the treatment of the disease had been removed.

In 1817 Pelletier isolated an alkaloid from ipecac which he named "emetin." It was later shown that this substance was in reality a mixture of three alkaloids. In 1894 Paul and Crownley demonstrated that the root contained a second alkaloid to which the term "cephaëlin" was given. Still later a third alkaloid, "psychotrin," was isolated and Pyman demonstrated that this alkaloid on reduction gives rise to "cephaëlin" and iso-cephaëlin. Another substance, the methyl ether of psychotrin, was shown to give rise to emetin and iso-emetin. Walters and Koch have experimented particularly with synthetic derivatives of cephaëlin, and found that cephaëlin-iso-amyl-ether-hydro-iodid was effective in destroying both the vegetative and the encysted amebæ in the intestinal tract of cats. Simon, however, found that in the treatment of human subjects it was of equal value to the simple alkaloids of ipecac in destroying the free living entameba, but that no definite effect could be noted in its action on the cysts. Psychotrin and methyl psychotrin, which are comparatively non-toxic, are said by Dale, Dobell, Jepps and Meakins to be therapeutically inactive in amebic dysentery. Low has also found that iso-emetin may be tolerated in large doses, but also does not produce any favorable therapeutic effect in this disease. The two most important alkaloids of ipecac in the treatment of amebic infections are emetin and cephaëlin. Emetin is a colorless, white powder which may become darker on exposure, is slightly soluble in water, readily soluble in alcohol, ether, chloroform, and benzene. The two salts which have been recommended for medical use are the hydrochlorid and the hydrobromid. The former has a greater solubility and is more applicable for general use. Pellini and Wallace in 1916 showed that this alkaloid depresses and may eventually paralyze the heart. Also, that it causes a definite derangement of metabolism, and is a powerful gastro-intestinal irritant, whether given by the mouth or by subcutaneous injection. Later experiments, however, have shown that when given subcutaneously in small doses the drug does not exert its emetic and expectorant properties. Cephaëlin, which is more toxic than emetin, is a colorless crystallin which is less soluble in ether than emetin, but is readily soluble in caustic alkali solutions. One salt is known, the hydrochlorid. While it has similar medical properties to emetin, it is a more powerful emetic and its subcutaneous administration is said to produce more irritation and pain at the site of puncture than emetin. Lake has emphasized the difficulty in the complete separation of emetin and cephaëlin, but he has also pointed out that, while the latter is more toxic, a fairly high per cent of it needs to be present to affect materially the toxicity of emetin. He also showed that the changes most often produced in experimental animals from toxic doses are acute degenerative changes in the parenchymatous organs. In spite of the large amount of work that has been performed upon the pharmacology of emetin, its exact action in the human body is still not certainly known. It obviously enters the blood-stream and, according to Mattei and Ribon, 1917, and Mattei, 1920, the greater part of it appears to be eliminated in the urine. Dale and Dobell have suggested that its specific action in human dysentery must be due to its action on the host and not on the parasite. They also believed that the drug was not particularly toxic when applied directly to the entamebæ and that it had absolutely no effect on clinical amebic dysentery in the cat. However, Vedder, Wherry, Bowman, the writer, and others, have demonstrated that both emetin and ipecacuanha have a decided effect in directly destroying amebæ and their cysts.[1] Dale more recently has curiously found that dimethoxy emetin is ten times as poisonous for the amebæ, and not nearly as poisonous for animals as emetin, but that it has no therapeutic effect whatever. Hence, it was concluded that the curative action of these alkaloids was proportional not to their direct poisonous action on the amebæ but to their poisonous action on the patient, and it is suggested that the body of the patient must play an essential and perhaps a primary part in the killing of the parasite. However, the experimental difficulties in connection with the chemotherapeutic study of emetin in cats infected with amebæ are considerable, and it is exceedingly desirable that the problem should be approached in other ways. The further study of the nature of the reaction between these chemotherapeutic agents and the cells of the patient and the final action upon the parasite is exceedingly important.

Since emetin is less toxic than cephaëlin, it has generally been employed in the treatment of amebic dysentery. While the best results in treatment have been obtained with it, it does not always bring about the destruction of all the amebæ or cause amebic ulcerations to heal immediately. Its curative action is often proportional to its early employment in the acute attack. In cases with advanced lesions where there is much destruction of tissue, and where secondary infection of the lesions with intestinal bacteria has occurred, its good effects are not so noticeable. Doses of ⅓ gr., thrice daily, or ½ gr., twice daily, of emetin hydrochlorid dissolved in sterile saline solution should be administered by hypodermic injection into the subcutaneous tissues for a week to ten days at a time. Children of eight years may be given ⅓ gr. daily, and younger children ⅙ gr. daily. Some observers have recommended that the injection be given intramuscularly, but Simon points out that the injection of the drug into the muscles is invariably followed by a sensation of soreness which may persist for many days. By the subcutaneous injection only occasionally is there a marked local reaction. Baermann and Heinemann have recommended considerably higher doses, but these are often dangerous, and doses of 0.3 to 0.4 gm. have produced very serious symptoms such as dyspnea, vascular paralysis, vomiting, thin stools, and a marked slowing of the pulse. A dose of 1 gr. (0.06 gm.) daily is usually within the margin of safety. Unless cases are treated for a week or ten days with emetin, relapses are very liable to occur. On the other hand the physician should bear in mind that the drug is poisonous and that there may be cumulative action. In patients who do not yield to treatment in a week or ten days, the drug should be interrupted for at least a short period before a second course of treatment is instituted. Kilgore has noted severe cases of peripheral neuritis after treatment with emetin. The trouble generally manifested itself in general muscular pains and in weakness, especially in the legs, going on sometimes to paresis. Wrist and toe-drop were common. The symptoms disappeared gradually on stopping the emetin. Severe neuritis was produced in one case from a dose of 19 gr., and in a second case from a dose of 6 gr. The latter patient obviously had a special idiosyncrasy for the drug. In recent years Levy and Rowntree, Johnson, Murphy, Velazco, Spehl, Collard, Balfour, and Pyman have all reported cases of poisoning due to emetin. Levy and Rowntree had one death in a man suffering from diarrhea who had received daily subcutaneous injections of 1½ gr. of emetin hydrochlorid over a period of twenty days, a total of 29 gr. In another case of poisoning, an anemic woman with pyorrhea alveolaris, 2 gr. were given in four days. The patient developed toxic delirium, with diarrhea, blood, and pus in the stools, but recovered. They have collected 20 cases of poisoning from the literature which they have tabulated. In six of these less than 10 gr. were given. All recovered except the first case. The symptoms included diarrhea with blood, diarrhea, peripheral neuritis, muscular paralysis and weakness, toxic delirium, and purpuric eruption. They emphasized the fact that patients differ markedly in their susceptibility to the drug, and that the various commercial preparations vary widely in toxicity. Lake, who has recently studied twelve market preparations, failed to find any considerable variation in the toxicity of them, but did find widely varying individual susceptibility of animals to the drug. Johnson and Murphy have also reported 2 deaths and 5 other cases of poisoning which they believe were due to emetin. The fatal cases had received in all 23½ and 25 gr. of emetin each in divided doses. In both cases muscular weakness was most pronounced and, in one, almost constant diarrhea occurred. In one, the necropsy findings showed pneumonia and bronchitis; in the other there was in addition fatty degeneration of the heart. In the 5 non-fatal cases, 3 showed diarrhea and all exhibited motor weakness and nervous disturbances. Evidence of some circulatory disturbance was noted in all. Diarrhea seems to be one of the most important symptoms of emetin poisoning. Therefore the physician should bear in mind that the diarrhea produced by large or prolonged doses of emetin may be confused with that produced by the dysenteric process. Hesse attributed the chief danger in emetin to contamination with strongly toxic cephaëlin, but, as intimated, Lake has more recently shown that a fairly high percentage of cephaëlin would need to be present to affect the toxicity materially. Hess, Lake, and Levy and Rowntree have shown that emetin has a very depressing action on the heart and circulation in toxic doses and the last-named authors have shown by electrocardiographic studies that the cardiac irregularity is due to fibrillation of the ventricles.

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[1] Sellards and Leiva have further confirmed these facts.

Rogers believes that 15 gr. of emetin will usually constitute a fatal dose for an adult man. Intravenous injection of the drug has been suggested, but it is more dangerous and is not recommended. One-half gr. has been given slowly in 100 c.c. of salt solution. If it is administered in this manner, the blood-pressure should be carefully observed during the injection.

All cases of amebic dysentery do not by any means yield to treatment with emetin, and relapses after the use of the drug in the doses recommended are not very uncommon. While the hypodermic administration of the drug in moderate doses causes no nausea or vomiting, as a rule, some observers believe that it is less efficacious when given in this way than when it is given orally. Wenyon and O'Connor have recommended a combined subcutaneous and oral administration of the drug. One gr. of emetin is given by injection in the morning and ½ gr. of emetin in tablet form at night. This treatment has been used especially in subacute and chronic cases. Various pharmacological experiments have been made with the object of reducing the nauseating and emetic effects of emetin, and at the same time retaining its efficient therapeutic action, but these have not yet been successful. Some observers, among them Simon, believe that it is more advisable to employ the whole drug ipecac rather than its isolated alkaloid emetin, and Manson-Bahr has also pointed out that the value of ipecacuanha in certain circumstances is still undoubted, and that it is still a question as to whether its having been superseded by emetin is wise or not.

The method of administration of ipecac by Manson was to interdict all food for three hours, then to give 10 or 20 drops of laudanum in a tablespoonful of water, and at the same time to apply a mustard poultice to the epigastrium. About twenty minutes later, when the patient is coming under the influence of the laudanum, 20 or 30 or even as much as 60 gr. of ipecacuanha in pill, bolus, capsule, or in suspension, in about one-half wineglassful of water, are administered. With a view to preventing vomiting, the patient is directed to lie flat on his back and to remain perfectly quiet for at least four hours. He must resist if possible the desire to vomit. Any saliva which collects in the mouth must not be swallowed but removed with a handkerchief or gauze. Should the ipecacuanha be vomited within an hour of its being swallowed, it is recommended that the dose be repeated as soon as the nausea has subsided. Salol-coated ipecac pills have been particularly used in America. Stitt has recently had success in avoiding nausea and vomiting by the administration of ipecac by the duodenal tube. Alcresta is the trade name applied to an absorption compound of the ipecac alkaloids or of emetin alone with hydrated aluminum salicylate. While a preparation of Fuller's earth causes little or no vomiting, due probably to the insolubility of the alkaloids in this form, the results in treatment with it are said to have been far less satisfactory than those obtained with emetin.

Emetin Bismuth Iodid.—For those cases of amebic dysentery which do not yield to emetin treatment alone, the double iodid of emetin and bismuth has been recommended. Dumez was first to suggest the employment of this preparation for the treatment of amebic dysentery. It is formed by the precipitation of soluble emetin salts with Dragendorff's reagent. It appears that thorough treatment with this drug will certainly cure many cases of the disease. It should be given by the mouth, enclosed in a gelatin capsule or paper cachet, in doses not exceeding 3 gr. a day for twelve successive nights. During the twelve-day course of treatment the patient should remain in bed and be given a liquid diet. While it has been stated that it has no action in the stomach, as it is insoluble in dilute acid, nausea, vomiting, and even slight purging sometimes occur after its administration. The substance is an almost insoluble brick red powder, and the emetin is gradually liberated in the alkaline juices of the intestine. It is, therefore, very important that it should not be made into a hard tablet or pill. This treatment in the doses suggested above does not, as a rule, give rise to symptoms of emetin poisoning. If after the administration of the 12 gr. the examination of the feces shows that the patient is still unaffected, the patient may be given a double course of treatment, 3 gr. daily for twenty-four consecutive days, provided of course that no unfavorable symptoms appear. Although many individuals infected with Entameba histolytica can be rid of their infections by means of this treatment, others appear to be quite unaffected by it. Simon has recently pointed out that it is not probable that this remedy possesses any special virtue in entamebic infections entitling it to the fulsome praise which it has recently received in the treatment of carriers, and that the same methods should be used in treatment of the carrier as have proved successful in the treatment of all chronic infections with the organism.

For the treatment of cases refractory to emetin a number of other preparations have also been recommended.

Bismuth Subnitrate.—This has been strongly advocated for many years, especially by Deeks, who recommends its use in heroic dosage. He gives a heaped teaspoonful, equivalent to about 180 gr. by weight, mechanically suspended in almost a tumbler of plain, or better effervescent, water, every three hours, night and day in severe cases, only lessening the amount when improvement takes place. The mechanical suspension in a large amount of water is essential, otherwise, it is prone to form a paste or solid mass, thus lessening its physiological effect. When the stools begin to lessen in number, and the tongue becomes clean, the number of doses is lessened to three or four daily. In very chronic cases he believes it wise to continue one or two doses daily for a month after convalescence is established. James has since advised the giving of the bismuth in these doses not alone, but combined with emetin to the point of physiological reaction. Connor has also employed this treatment in more than 100 amebic dysentery cases, only one of which has relapsed. In addition to the medical treatment, a normal saline irrigation was given twice daily when there was evidence of an extensive colitis. Just how bismuth acts in amebic dysentery is not entirely clear. Darling's experiment demonstrated that it was not toxic for free living amebæ. Mix has suggested that the destruction of the entamebæ may be due to the fact that bismuth subnitrate in large doses takes up sulphur as fast as it is formed in the intestinal tract. This causes a decrease in the amount of nascent hydrogen sulphid which is said to be essential to the life of the amebæ.

Chapparo Amargoso.—This is the Mexican name for a simarubaceous plant, Castela nicholsoni. It was recommended for the treatment of dysentery by Putegnat, of Brownsville, Texas, in 1883, and subsequently by J. W. Nixon, West, Crittenden, P. I. Nixon, Shepheard and Lillie, Sellards and McIver, and others, for the treatment of amebic dysentery. Chapparo amargoso is a small thorny bush which grows without cultivation on dry, rocky soils, particularly in the hilly sections of southwest Texas and northern Mexico. The drug has been employed either in the form of an infusion or as a fluid extract. The latter preparation has been placed upon the market. It has been recommended that the infusion be administered in doses of from 6 to 8 ounces, three times a day, preferably before meals, for an indefinite period or until the patient has been relieved. The fluid extract may be employed in doses of 1 or 2 teaspoonfuls, likewise before meals, three times a day. Rectal injections of the infusion are also recommended in conjunction with the administration of the drug by the mouth. Shepheard and Lillie, who treated 4 cases with a crystalline bitter principle which was obtained from the drug, found it inactive, as none of the 4 cases treated were cured. However, Sellards and McIver have reported successful treatment of 4 cases with the active principle of this drug which was prepared by extracting the crude plant with methyl alcohol.

The use of another plant of this same family Simaruba has also been reported upon favorably in the treatment of amebic dysentery by Yersin, Breaudat, Lalung-Bonnaire, Shepheard and Lillie, and Mayer.

Kosam.—This is the name given to a preparation from the seeds of another simarubaceous plant and has also been recommended for the treatment and cure of amebic dysentery by Menetrier, Brodin, Galliard, and Brumpt. It seems possible that all these plants may contain a common principle other than the tannin present. Barger has obtained a crystalline bitter principle from simaruba, but this seems to have doubtful therapeutic action, as does the one obtained by Ewins from chapparo.

Oil of Chenopodium.—Walker and Emrich have suggested oil of chenopodium in 16 minim doses, given in gelatin capsules at 8 and 10 A. M. and 12 M., for the treatment of carriers of Entameba histolytica.

Emphasis is laid on the necessity for preliminary purgation with magnesium sulphate and the treatment is followed by castor oil, 1 ounce, containing 50 minims of chloroform. Barnes and Cort have also employed this treatment with good results, but in a few cases improvement was not evident or was only temporary.

Salvarsan and Neosalvarsan.—Recently successful treatment of obstinate cases of amebic dysentery has been reported from the use of salvarsan and neosalvarsan by Mink, Ravaut, Krolunitsky, and Calame. The drug has been recommended intravenously and in chronic cases orally in capsules, each containing ¾ gr. (0.05 gm.) of the drug. Rectal injections have also been administered with satisfactory results. Ravaut recommends a combined treatment with neosalvarsan and powdered ipecac. Tannin and benzyl benzoate have also been recommended. However, a number of these drugs have not been sufficiently tried as yet for us to form a definite opinion in regard to their value.

Other Preparations.—Among the most recent preparations recommended may be mentioned uzara, said to be derived from an African plant of the family Asclepiadaceæ, and amibiasin, an alcohol extract of the bark of Garcinia mangoastana. Amibiasin has been particularly used by Ditlevsen for the eradication of cysts. Brown, 1922, has recently called attention to the action of conessin, an alkaloid having the formula $C_{12}H_{20}N$, which has been isolated from several members of the natural order Apocynaceæ. It has been obtained from Holarrhenica antidysenterica in India and from Holarrhenica congolensis in the Belgian Congo. Infusions of the seeds of these plants have long been used with success in the treatment of chronic dysentery. The author found that this substance could be administered by the mouth in suitable doses without producing untoward symptoms, and experiments upon mice proved it to be 50 per cent less toxic than emetin. When injected subcutaneously, however, it produces locally an area of necrosis. In a dilution of 1 part in 1,000,000, conessin sulphate inhibited the growth of fresh-water amebæ. Two substances known as yatren and emetren, the latter a combination of emetin hydrochlorid and yatren, have very recently been recommended for treatment. The use of the former is discussed in the second paragraph under Local Treatment.

Adrenalin.—Adrenalin has also been recommended in the treatment of the disease by Bayma and Von Groeer, who have claimed success in the cases in which it was employed. From 10 to 20 drops of a 1 : 1,000 solution have been given by mouth every two hours with daily enemas of 2 liters of saline 1 : 1,000,000 or 1 : 1,500,000 in strength, without harmful effect. Remlinger and Dumas have emphasized the importance of such treatment in those cases of chronic and prolonged dysenteric infection where the suprarenal syndrome exists. Secondary bacterial infection of the ulcers with various bacteria which may occur in the intestine often occurs in amebic dysentery. Thorium sulphate, 4 to 6 gm. daily by the mouth in a cachet and a daily injection of 200 c.c. of a 2 per cent solution of the same salt, has been suggested by Frouin, but with this substance, as with a number of others, no thorough trial has been given.

Local Treatment

Cases with extensive lesions of the colon in which the symptoms are not very acute are often favorably affected by treatment with rectal injections and irrigations of the large bowel. The purpose of such treatment may be not only the destruction of the amebæ, but also the flushing out of the colon and cleansing the surface of the lesions. Rectal injections of quinin sulphate or quinin muriate, 1: 1,000 or 1: 2.500, are particularly recommended. Protargol solution, 1: 500, has also been employed. The solution should be allowed to enter slowly by gravity through a long rectal tube previously lubricated with vaselin or oil, and the tube should be passed to its full length or as high as possible. The amount injected should be between 1 and 2 liters. Sometimes cases yield to such treatment with the quinin solutions that have not been benefited by other treatment. It has been repeatedly demonstrated that quinin has amebicidal properties. Obviously it is when the ulceration is in the lower part of the colon that the results of such treatment are particularly favorable. As the mere flushing out and cleansing of the colon often aids in the treatment, normal saline solution may at times be substituted for the quinin solution, particularly in cases where the latter causes intestinal irritation. Recently Van der Togt has tried to destroy amebæ in the colon by increasing the osmotic tension in the bowel contents to a degree harmful to the amebæ. Sodium chlorid and soda are obviously too irritating in high concentrations for this purpose. However, enemata of 20 to 40 per cent cane sugar solutions given twice daily for eight consecutive days are said to have cured a large number of cases. In only 1 case did the amebæ fail to disappear definitely. When ulcers exist in the rectum, and there is much tenesmus, local treatment with argyrol or some other astringent or antiseptic substance may be applied through the speculum after the administration of a small enema containing cocain or morphin. Manson-Bahr and Gregg (1921) have employed the use of the sigmoidoscope both as an aid to diagnosis and to treatment in amebic dysentery. Enemas of starch and opium sometimes have a very soothing effect. In connection with treatment, radioscopy has sometimes been employed in determining the localization of the larger ulcers, bismuth subnitrate being administered for several days before the photograph is taken with the hope that it will localize particularly in the lesions. Stitt recommends the operation of appendicostomy, following which a catheter is inserted and the large intestine irrigated with a 1 per cent solution of bicarbonate of soda to wash away the mucus; later a boric acid solution may be employed. Castellani and Müller also recommend appendicostomy and irrigation in gangrenous cases. Phillips, however, is not enthusiastic in regard to this treatment and points out that its success has not been very great in many cases. Ross states that appendicostomy did not give encouraging results during the World War.

Muhlens and Menk, in discussing the results of ten years experience in the tropical institute in Hamburg, remark that appendicostomy and even cecostomy and subsequent lavage of the large bowel certainly ameliorate the condition but do not accelerate the healing of the ulcerations. They particularly recommend a substance called "yatren" for treatment. This substance consists of 5 parts of iodin, 8 of oxychinolin, and 7 of sulphate of soda. It is said to possess high bactericidal properties without destroying tissues, and at the same time acts as a cell stimulant. The first attempts with it were made with 2 especially resistant cases which after months of emetin treatment had undergone appendicostomy and cecostomy without success. In both instances an almost immediate clinical improvement took place. In 6 other resistant cases subsequently treated, a similar remarkable improvement took place. If on sigmoidoscopic examination ulceration is present, they advise that 200 c.c. of a 2½ to 5 per cent solution of yatren should be introduced through a rectal tube in the usual manner. If the absorption of the solution is taking place satisfactorily, it can be satisfactorily proved by means of the iron perchlorid test of the urine. It is also recommended that the yatren be given in powdered form in capsules or pills in 1-gm. doses three times a day. Keratin-coated pills are also well borne. Intramuscular injection of 10 c.c. of a 5 per cent solution produced no undue reaction. For the treatment of a case they suggest eight to fourteen days with enemata or doses by the mouth with sigmoidoscopic and microscopic controls; after a week's interval a repetition of the treatment for from three to seven days; after another equal interval a further course of treatment for from three to five days. During this treatment there must be absolute rest and strict diet.

Treatment of Complications

The complications of amebic dysentery requiring special treatment include amebic abscess of the liver, lung, and brain, peritonitis, and severe intestinal hemorrhage. In general it may be stated that when there is evidence of any of these complications a thorough course of treatment with emetin should be given. According to a number of authorities, the presuppurative stage of amebic hepatitis often responds to injections of emetin, and symptoms which almost certainly have denoted an abscess may all rapidly clear up and disappear under its influence. If, however, the signs of liver abscess are definite, and there is distinct evidence of pus formation, surgical treatment should be at once instituted and the abscess should be opened and freely drained, unless it has already perforated into the lung and is being freely discharged through a bronchus. After the abscess has been opened, it may be irrigated frequently with quinin solution, 1 : 1,000; or 2 ounces of an emetin solution, 1 : 1,000, may be injected into the cavity, hypodermic injections of emetin or emetin bismuth iodid by the mouth being employed at the same time. It is usually necessary for the surgeon to make exploratory punctures of the liver in order to locate the abscess. For this purpose, an aspirating needle of sufficient caliber to transmit the thick pus is advisable. Often many punctures in different parts of the liver must be made before the abscess is found. The surgeon must be prepared to operate immediately the abscess is located. These exploratory punctures of the liver are not entirely without danger, for fatal hemorrhage has sometimes followed them. With reference to the surgical procedures, Manson and Cantley advocate drainage of the abscess by means of a trocar and cannula. Rogers recommends aspiration of the pus and the injection of quinin solution or of emetin by means of a special trocar with a flexible silver sheath. More recently Charles and Cope have advised the open method of treatment with free incision.

General peritonitis or perforation of the bowel demands surgical aid if the condition of the patient warrants it. Abdominal section is advisable in those cases in which the general condition of the patient is good and the symptoms of perforation acute. On the other hand, when the general condition is bad or indifferent, non-intervention is frequently justified since patients with perforations sometimes recover without operation, the escape of the contents of the gut being often prevented or limited by adhesions. Also the bowel wall is frequently friable and unsuitable for suture. In connection with the occurrence of amebic appendicitis, the surgeon should bear in mind that, in those cases in which the appendix is ulcerated, the cecum is usually also extensively ulcerated. Local peritonitis without perforation requires rest and the application to the abdomen of ice or hot fomentations with opiates by the mouth.

Abscess of the lung requires the usual treatment with emetin. Amebic abscesses discharging freely through the lung or discharging externally are apparently often benefited by emetin treatment and may require no active surgical procedure. X-ray examinations may give information as to the advisability of surgical intervention for the better drainage in cases where the liver abscess has ruptured into the lung. If the abscess has opened into the pleura or empyema has resulted, resection of the ribs may be necessary to secure free drainage.

For the treatment of brain abscess, in addition to emetin, extensive trephining is advisable and the abscess should be sought for with a channeled sound and not with an aspiration needle, owing to the viscosity of the pus. When the abscess is localized, it should be opened. Morphia and bromids are indicated for the relief of headache and the other cerebral symptoms.

Postcolic abscesses and amebic abscesses in other organs such as the spleen or ovary or fallopian tube, as well as in the skin and adjacent tissues, may rarely also require surgical treatment.

For serious intestinal hemorrhage complete rest is demanded. Morphia should be given and ice applied locally to the abdomen. Stimulants and subcutaneous or intravenous injections should be employed only when their use is indicated by the symptoms. Adrenalin in doses of 1 to 1.5 c.c. of a 1:1,000 solution has been recommended, and the injection of a solution of calcium chlorid or of horse serum has occasionally given good results.

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CHAPTER XXXI

THE TREATMENT OF SYPHILIS

John H. Stokes

INTRODUCTION

The problems of the treatment of syphilis have increased enormously in complexity within a surprisingly brief period. Two decades ago, in ignorance of the actual cause of the disease and without other than symptomatic guides for diagnosis and treatment, rationalization was impossible. The advent of experimental methods, the possibility of the laboratory study of the life habits and reactions of the Spirochæta pallida, the advance in our knowledge of microscopic pathology and the application of serologic methods to both diagnosis and treatment, have illuminated the field, and new possibilities for radical cure, for control of infectiousness, and for miraculous symptomatic results have multiplied without number before our eyes. Far from being simplified, the situation is to-day, in many respects, more complex than ever before. Yet this complexity is relieved by the hopefulness which comes from increasing soundness of knowledge.

The problem of the treatment of syphilis to-day is one of rationalization. In the days when we knew little or nothing of the actual cause, saw only results, and accepted a large measure of our ignorance as inevitable, it was a comparatively simple matter to outline a system of treatment for the disease. In those days, "How do you treat syphilis?" was a fair question. In these days, to appreciate the answer to such a question, one must have a knowledge of the disease, which is unfortunately lacking in the professional training of too many men. This knowledge answers the question "Why do you treat syphilis?" The problem of syphilotherapy is to teach physicians *why* they treat syphilis in thus and such ways rather than *how,* because the *how* is so variable that no exercise of the ability to learn by rote can ever take the place of a comprehension of the reason why.

With the growing complexity of our knowledge of syphilis, specialism will be inevitable. To be sure, not all patients with syphilis, or in fact no more, perhaps, than a small proportion of them will ultimately receive personal treatment at the hands of experts. In this respect, the situation does not differ from that of any other therapeutic problem in internal medicine. Syphilis should be treated by the general practitioner, systematically, thoroughly and exhaustively. Time and experience will more precisely define the methods of therapeutic approach in this disease. The general practitioner will, I believe, ultimately work as a coöperator with the specialist in treating syphilis and to some extent under direction. He will administer treatment, and he will comprehend the rationale of the measures which he applies. But in the maintenance of record, in systematized observation, in special and difficult diagnostic procedures and in certain difficult forms of treatment, he will seek advice. This advice will be available for certain types of cases in therapeutic centers, and for others in the offices of specialists. It has become exceedingly difficult for any man acting alone to give the patient with syphilis all that is his due.

This account of the treatment of syphilis is written, therefore, with the two foregoing considerations in mind. Its aim is to rationalize the treatment of syphilis, to sketch broad outlines of various aspects of the disease and its complications for the practitioner, and to describe in detail those procedures which he can and should systematically apply in the treatment of the disease. Procedures such as the intraspinal treatment of neurosyphilis, and even, under certain circumstances, the systematic use of the spinal fluid examination as a therapeutic control, are the legitimate domain of the expert and the advisory center. For this reason no attempt is made here to discuss their technic.

Many critical situations are being introduced into the modern problem of syphilis by the physician inadequately trained with respect to syphilis and the inadequately treated patient. These will be pointed out in somewhat greater detail later. The emphasis here must be placed on the fact that the day is past when any man in any place, who can command protiodid pills and iodid of potash, can treat syphilis after the technic of the masters. In spite of this radical change in the methods and availability of treatment, the reaction of certain general practitioners still remains that of the last generation. There is too often the tendency to resent suggestion, to regard the situation as trivial, or to take a short-range view of the problem. The physician who undertakes to treat syphilis at the present day should master the essentials of modern technic by sufficiently persistent study and practice and, having done this, should look to suitable consultant experience precisely as in surgery for the complex judgment and decisions ultimately involved. If he does not care to do this, he should refer his syphilologic work elsewhere.

As in every growing field, therapeutic experimentalism in new drugs and procedures claims a large share of the physician's attention. The practitioner should not be too easily led to follow every new claim.

Enough work has been done in the past two decades to make certain fundamentals of effective treatment reasonably clear. To these fundamentals the average physician should pin his faith. He is far wiser to have learned one drug and one system of treatment thoroughly than to have drifted this way and that under hearsay influences, trying X's this and Y's that, under no guidance other than a blind impulse toward change. The effort in this presentation will be to describe what may be called approximately standard methods, which yield as high a proportion of good results as can be expected within the limits of the present comprehension of syphilis as a disease. Inevitably the account will be tinged by the experience of the Section of Dermatology and Syphilology of the Mayo Clinic.

THE IMMUNOLOGIC AND PATHOLOGIC BACKGROUND OF SYPHILOTHERAPY

Into every syphilitic infection there enter four elements. The first of these is the causative organism of the disease, its physical, chemical and bacteriologic characteristics. The second is the host on whom the infection is implanted. On his peculiarities as a soil will depend as much of the clinical picture and therapeutic response as on the Spirochæta pallida as seed. Every syphilitic infection, representing as it does an implantation of a seed on a soil, yields a crop. This crop is proportional to the third element, consisting of certain accessory factors besides the seed and the soil. Among these accessory factors should be numbered time, intercurrent infection and other incidents, such as trauma, pregnancy, and activity of the physiologic defense. Some of these elements are controllable, others are not. The fourth element in determining the course of a syphilitic infection is treatment. It will be apparent, therefore, that the physician, as he confronts his patient, holds in his hand only one-fourth, or at most one-third, of the power to command the situation. That the situation yields so often to a minority influence in behalf of the patient is a crowning tribute to the "treatability" of syphilis as a disease.

The existence of strains or types of the Spirochæta pallida, virulent and weak strains, or strains with a predisposition toward special types of structural involvement akin to elective localization, is generally accepted. Variations in activity and virulence dependent on the rate of growth of the organism at the time of transplantation have been suggested by many aspects of clinical and laboratory work, but have not as yet been fully confirmed.

The influence of the peculiarities of the individual host on the course of a syphilitic infection is only gradually coming to recognition. There is about these peculiarities an "unpredictability" which thus far has yielded too little to investigation. Experimentally, it appears that certain hosts, such as the rabbit, are for entirely unknown reasons somewhat more resistant to infection during certain seasons of the year. It is well known clinically that certain patients and certain types of infection do not present certain complications. The impression is growing that the development of neurosyphilitic complications is a function ascribable to some extent to unknown predispositions on the part of host as well as of organism. The combination of a predisposed patient and a highly adapted strain of organism has a fatal quality and makes inevitable the ultimately disastrous outcome of an as yet unknown proportion of infections. Special resistance to syphilis extends to the total immunity of certain animals and even to the suspected occasional and temporary immunity of man. Once infection has taken place, an acquired resistive quality on the part of the host develops. Reinoculation of the Spirochæta pallida on an untreated human syphilitic host in the earlier stages of the disease can be accomplished only with the greatest difficulty, and in fact rarely takes place. There develops in the infected individual an antagonistic physicochemical mechanism, spoken of as the physiologic defense, which must be repeatedly taken into account in the succeeding discussion of treatment.

The most widely accepted acccessory factors in determining the course of a syphilitic infection are the influence of the site of inoculation, the effect of intercurrent infection, of pregnancy, of sex, of time, of wear and tear on the patient, and of trauma, all of which will be discussed in their special relations.

Under the general head of treatment it is proper to include the effect of medicaments, sufficiently or insufficiently used, or used to excess, and of controllable intercurrent accidents affecting the course of the disease, such as the general hygiene of the patient, the use of alcohol and the avoidance of overstrain.

The belief that syphilis is a purely local disease for an appreciable time after its onset has been an important influence on therapy, particularly during the earlier years of the use of arsphenamin. In fact, it was on this conception that the idea of abortive cure was founded. While the conception of abortive cure is undoubtedly in part sound, it has been applied with too little discrimination to the treatment of early syphilis. Within a year or two after the recognition of the Spirochæta pallida in 1905, Neisser and his collaborators in their Javanese work had shown that syphilitic infection became general within a few hours after inoculation. While the chancre is unquestionably the primary tissue reaction at the site of invasion, it is not evidence that the infection has remained localized at its point of entry. A syphilitic is probably a syphilitic through and through within forty-eight hours after the organism has gained access to the body. The recovery of the Spirochæta pallida from the splenic pulp, bone marrow, testes, and other visceral structures in the ape within the first days of the incubation period should have made it apparent that syphilis presents the therapeutic problem of a general infection from the first moment of invasion. It should, therefore, always be attacked by general and not by local measures, no matter how early it is recognized, and therapy should be persisted in for the long period which experience has taught as essential in the management of the clinically obvious, fully established infection. Neisser's work remained relatively little appreciated by clinical syphilolographers in this country. Reasoner, and Brown and Pearce, however, have revived the issue in a way to impress this point more effectually on the medical profession. These authors have shown that even castration within forty-eight hours following the inoculation of the rabbit testis with Spirochæta pallida will not prevent the general infection of the animal. Within one week after inoculation, and before any signs of local reaction occur, the blood of the inoculated animal becomes so heavily infected that 0.5 c.c. will transmit the disease.

In order, then, to comprehend and apply modern methods to the therapy of syphilis *it must be recognized as a first principle that syphilis is a systemic infection for days and even weeks before the appearance of the chancre.* An effective therapeutic attack must, therefore, seek always to diminish the lead of infection over treatment by the use of every possible aid toward early diagnosis.

Systematic study of the pathologic reaction of the tissues of the body has shown quite plainly that, while syphilis is a systemic disease, it has a highly significant local phase. The chancre is a type of local tissue reaction to the invading organism. As the disease progresses this reaction is repeated in miniature in thousands, ultimately probably in millions, of individual foci throughout the body. The cycle of reaction presents a singular uniformity in all of these varied types of lesions. Local invasion of the perivascular lymphatics by the Spirochæta pallida results in a vascular reaction, assuming presently the form of obliterative endarteritis with perivascular infiltration and proliferation of the connective tissue elements. This elementary process occurs in practically every type of syphilitic lesion. If the life cycle of the organisms is studied in such a lesion during its early period of development, steady and rapid increase in their number can be easily recognized. As the number of organisms increases, the escape of larger and larger numbers into the surrounding lymphatics and into the blood-stream becomes inevitable. At the height of its development, each individual focus becomes a distributor of organisms to its lymphatic drainage area and to the vascular system as a whole. Having reached this height of development, histologic changes characteristic of regression and healing can be recognized. Hand in hand with them, the number and viability of the organisms in the focus can be seen to decrease.

The reaction which culminates in healing may finally exterminate all the organisms in a lesion. More commonly, however, healing, while structurally complete, is not bacteriologically so. Certain surviving organisms remain in the scar or surrounding tissue, perhaps completely inhibited for the time being, but ultimately destined to begin multiplication again when the tissue immunity due to reaction wears off. The life story of active syphilis, therefore, becomes one of successive cycles of invasion of tissue by the organisms: spirochete reproduction with the establishment of new foci by contiguity or by spread through blood or lymph, then tissue reaction, healing, destruction of many but perhaps not all the organisms, followed by a period of quiescence or latency, and then a resumption of the cycle in the form of relapse. The original local reaction is at the site of the chancre. Treatment beginning at that time may be carried to the point of inducing healing of the visible focus, and even to the complete extermination of the spirochetes in that focus. Yet the complete visible recovery at the site of the chancre, or of the secondary eruption if treatment is begun later, does not mean the destruction of every organism in all other foci in the body. Various tissues, there is reason to believe, differ in their ability to develop enough local resistance to destroy the organisms which invade them. The nervous system, according to the suppositions of Fraser and Duncan, for example, has relatively little power to oppose a physiologic resistance to the organisms which reach it from other foci. If treatment is not given in sufficient amount to destroy the organisms in this defenseless tissue, relapse will occur sooner and more violently in that tissue than in others when treatment is suspended. Other foci, especially in the spleen and the lymph-nodes, seem to harbor organisms or act as reservoirs more readily than do others. From them perhaps, long after the infection is reduced to inactivity elsewhere in the body, come new but invisible flare-ups of local lesions to distribute spirochetes by the blood and lymph for new generalizations of the infection and clinically recognizable relapses.

The activity of a syphilitic infection is then punctuated by periods of quiescence. This quiescence may be induced by treatment, to be sure, but it can also be induced without treatment by the action of the defense mechanism already mentioned. Systemic defense in syphilis unfortunately does not have the intensity it has in acute infections, in which the reaction suppresses the disease or the patient dies. It may serve to hold the infection in check for varying periods, and in a probably small proportion of cases may induce spontaneous cure. But as a rule it suffices simply for the disappearance of gross active lesions, leaving an inflammatory residuum, the slow fibrotic changes of which are responsible for the degenerative lesions of late syphilis. A combination of clinical and laboratory observations have indicated that certain tissues of the body, and especially the skin and the bones, play an important part in the development of the active defense. The passive defense, so to speak, in Warthin's opinion, is maintained in the parenchyma of all the important structures of the body in the form of a microscopic reaction around small groups of spirochetes, largely in association with the capillaries. Histologically a small accumulation of lymphocytes and an endarteritis followed by fibrosis may be the extent of the process, which may endure for years. But that fibrosis in which it terminates represents a replacement of parenchyma by an indifferent and weaker tissue. If the replacement occurs in the wall of the aorta, weakening with ultimate sacculation and the development of aneurysm may be the result. If it occurs in the muscle of the heart, disturbances of conduction and ultimate myocardial failure from loss of muscle tissue is the result. If it occurs in the liver, the result is a cirrhosis; if in the brain, the result may be paresis. It is apparent, therefore, that the latency which is maintained by chronic inflammatory reaction in parenchymatous tissue is purchased at a price which is high in proportion to the rate at which the parenchyma is used. Every syphilitic patient who has reached the point where he no longer has an active lesion is open to the suspicion of living on his parenchyma, so to speak, which is maintaining him symptomless at the price of its inflammatory degeneration.

The story of latency in syphilis is not completely told with the discussion of osseous and cutaneous defense and parenchymatous degeneration. There is unquestionably a type of latency in which, without visible inflammatory reaction in the surrounding tissue, a focus of spirochetes can be held completely in check, apparently incapable even of reproduction without visible impairment of the integrity of the tissue in which they are lodged. This, for example, may be seen in the muscle of the heart in herodosyphilis which, in the absence of visible degeneration or impairment of function, may yet be a veritable harboring place for the organisms. To what extent this absolute latency, this reduction of all the spirochetes in the body to complete innocuousness, occurs in clinical practice, it is as yet impossible to determine. There is little doubt that it occurs and that it is responsible for spontaneous cures and for the innocence of some undoubted infections. Probably all patients with syphilis experience periods of true latency in which they maintain a perfect balance with their invaders for a time, only to lose it for periods in which adverse conditions reduce tissue resistance to a point at which the organisms can again become pathogenic and able to reproduce.

In the existence of latency, then, syphilotherapy confronts problems quite as important as those which concern the control of the active lesion. It may be comparatively easy to stimulate the body to the point of controlling an active process and bringing about the healing of a chancre, a secondary lesion or a gumma. It may be possible to accomplish healing by the extermination of the spirochetes outright with a spirillicide. But what is to be done with the patient who is keeping himself free from symptoms? Are we to rush in with therapeutic agents which may upset his immunity balance, or shall we leave him to his own devices? The problem would be a simple one if we could tell, before signs of degeneration appear, just what he has been doing with his defense mechanism and how it has been working. If he has maintained a true asymptomatic latency, without parenchymatous inflammatory reaction, we may well leave him to the maintenance of that condition by his own internal forces. But if he has been paying out parenchymatous capital bit by bit, so to speak, in the form of this inflammatory defense which Warthin has emphasized, we may find him showing the first clinical signs of irremediable degenerative damage in the forties or fifties.

There does not exist any method of appraising the status or the type of defensive mechanism which a patient is employing in the maintenance of his latency. The Wassermann reaction certainly cannot be trusted as an indicator of the state of the physiologic defense, for it is often negative in the presence of both progressive active and degenerative lesions. The mere appearance of good health, reënforced by the ordinary physical examination, cannot demonstrate the condition of the minute foci in the wall of the aorta, in the liver and other structures, on which the patient may be depending for the specious appearance of health which may eventuate in the gravest degenerative lesions. The application of these questions to the therapeutic management of latency will be considered in its proper place.

Modern conceptions of the infectiousness of syphilis are important guides to treatment. The infectiousness of the early lesions of the disease was, of course, clinically understood long before the discovery of the Spirochæta pallida. With the development of experimental syphilology it has been possible to show that the blood is infectious during the period of development of the primary lesion and the secondary eruption, and that it may be infectious in latency. The secretions of glands are not infectious unless they come in contact with open lesions, except the milk of a nursing mother in an active stage of the disease. Closed or dry lesions are not infectious, but abrasion or moisture may render them so. An important contribution was made by Eberson and Engman recently in the demonstration of the infectiousness of the semen of the latent syphilitic. In one of their cases the infection was of many years' standing, had been treated with arsphenamin, and was Wassermann positive only with a sensitive cholesterinized antigen.

Clinical experience has in general supported the belief that, for practical purposes, syphilis tends to become non-infectious toward the fifth year of the disease, and that after that period the patient need no longer be regarded as a dangerous carrier. Just how much revision of this rule such results as Eberson's may compel, it is as yet impossible to say. The influence of pregnancy and lactation has a very important bearing on latency in women. The suppression of lesions which they induce may, by producing a spurious cure, permit the subsequent infection of other pregnancies, in spite of the apparent health of the mother. The infectiousness of late syphilis, so far as practice is concerned, has long been known to be almost negligible, although positive animal inoculation is possible from practically all of the lesions of untreated late syphilis.

The control of the syphilitic carrier under the old régime has been a problem without a solution. Time and good advice were the physician's most effective weapons. Mercury and iodid, as will be apparent in the discussion of the rationale of their use, are seriously deficient in power to control infectious recurrences, and, by the relatively ineffective methods of administration by mouth in use in the past, left the disease to run largely its physiologic course in this regard. The advent of the arsphenamins has altered the situation materially, and it is now reasonably assured that, while under treatment with this drug and for some weeks thereafter, the great majority of patients are non-infectious. Moreover, a much larger proportion than ever before are promptly removed from the ranks of carriers by the radical cure of their infection in the early weeks of its course. On the other hand, it must not be forgotten that arsphenamin has not done away with relapse, and that its ineffective application, by inducing a false appearance of cure, has really made relapse in certain types of cases more frequent and more dangerous than ever before. But this cannot, of course, be laid at the door of the drug per se, but of those physicians who are not properly schooled in its use.

The immunologic background of late syphilis, with its inflammatory and degenerative defense mechanism, emerges gradually from that of latent syphilis. A number of observers, beginning with Finger and Neisser, have felt that all the phenomena of late syphilis could not, however, be fully explained simply on the basis of vascular reactions and slow degenerations of the parenchyma of important structures. The formation of gumma, in particular, seems to involve an additional factor of allergy or tissue hypersensitiveness which they designated "Umstimmung." This allergy gradually develops in the course of an unknown proportion of the ordinary, slowly progressive infections, and manifests itself in a violent local reactivity of some tissue, presumably to the presence of a small focus of spirochetes. Around this spirochetal focus there develops a tremendous granulomatous hyperplasia, known as the gumma, a violent inflammatory reaction out of all proportion to the number of spirochetes detectable at its periphery. Central necrosis may occur, with extensive ulcerative and destructive changes. This type of allergic reaction is responsible for the gross tissue damage and defects which develop in such structures as the skin, the bones, and the liver in late syphilis. The process is different, in degree, rather than in character, from the simpler slow, inflammatory focal changes that are responsible for the degenerative lesions. The difference in degree is apparently the result of a difference in the reaction of the tissues rather than in the organisms. It is interesting that the changes that occur in the luetin reaction are apparently those that occur in the gumma, and that the reaction is apparently non-specific in character and may be induced by other agents than the Spirochæta pallida as such.

Allergy is particularly important from the standpoint of the therapist because it may be artificially induced by inadequate treatment, as Gennerich and others have shown. A sudden destruction of large numbers of organisms with arsphenamin, when not followed by proper resistance-building treatment, seems to leave the body not only deprived of physiologic defense but actually hypersusceptible. The reappearance of the organisms at the first relapse results in the development of late lesions within a few months of the onset of the infection. It is in this way that we encounter enormous gummas of the skin and bones, brain gummas, violent meningeal recurrences, and so forth, years before their chronologic sequence in the ordinary course of the disease. The possibility of production of a premature allergy must, therefore, be borne in mind as one of the dangers of the ineffective use of the arsphenamins.

Modern treatment for syphilis influences resistance in another way than the possible development of allergic hypersusceptibility. Physiologic defense in syphilis depends on the presence in the tissues of the Spirochæta pallida. While the organism is in contact with the tissue, the tissue is stimulated to develop the means of both local and general resistance. If the Spirochæta pallida is removed abruptly from the tissues, no resistance will develop. In the days of mixed treatment by mouth, removal of the Spirochæta pallida from the tissues in toto by means other than the development of tissue reaction was impossible. With the development of the arsphenamins, however, it has apparently become possible literally to remove the Spirochæta pallida from the tissues without stimulating them to build up a lasting physiologic defense. Spirillicidal agents have, therefore, paved the way toward a species of non-resistance toward syphilis which may constitute an extremely serious therapeutic problem. The problem becomes serious when the amount of arsphenamin given is insufficient to destroy completely every organism in every focus in the body. If sterilizing treatment accomplishes its purpose of complete extermination, there is, of course, no need for tissue or general resistance. On the other hand, suppose that arsphenamin destroys all the spirochetes in the body except those around the dural sheath of the seventh nerve. These spirochetes, imbedded in tissue with a poor blood supply and low local resistance-producing capacity, are thus freed from the controlling influence of antibodies brought to them from other tissues by the blood, and are left to reproduce at will. The result is a sudden, highly localized flare-up of seventh nerve paralysis coming apparently from a clear sky in a supposedly cured case. This is Ehrlich's explanation of the mechanism of those neurorecurrences after inadequate treatment, which have been the cause of so much concern to syphilotherapists during the past decade. The effect of the arsphenamin phase of modern treatment in destroying the spirochetal source of bodily resistance to the disease without supplying an adequate substitute is, therefore, a highly important consideration in the planning of treatment.

It will be apparent that I have thus far given little attention to the minute description of the various stages of syphilis, primary, secondary, tertiary and quarternary or parasyphilis, which formed the starting point for the older treatises. Such differentiations were essentially morphologic rather than physiologic, so to speak, and are not adaptable to the modern comprehension of the life story of the disease. There exist differences between early and late syphilis which I have tried to emphasize. But the most effective comprehension of the situation does not come from an effort to fit the morbid phenomena of action and reaction, the cycles of flare-up, cure and relapse, the play of organism on host, and host on organism, into the rigid forms of the older classification. It is much better to try to comprehend in syphilis the movement of the process as a whole, the resistance which may be counted on as a therapeutic ally, the shortcomings of defense which must be bolstered up with our medicaments, the prevention of degenerations and the protection of others from the infection.

PROGNOSIS OF SYPHILIS

Enough has been said in the discussion of fundamentals to indicate that syphilis is the relapsing disease par excellence. Relapse is so much a part of the physiologic and pathologic cycle of action and reaction that it should become fundamental to the mental attitude of the syphilotherapist to expect it and to be on the lookout for it. This expectation of relapse should be carried in the background of the mind, no matter how good or how promising the immediate therapeutic response. This cautious alertness toward relapse should go hand in hand with the alert suspiciousness of the mind which is the best mental equipment for the diagnosis of the disease. Yet this therapeutic cautiousness should never degenerate into an uncritical pessimism. The tradition that syphilis is cured only by death should no longer dull the effectiveness of the therapeutic attack.

One of the most important influences affecting prognosis is that of time. The time which has elapsed from the onset of the infection until the diagnosis is made is the first and most important fact in the clinical management of the disease. There is no more instructive lesson in medicine than the contrast between the leisurely clinical weighing of gradually developing early signs and symptoms, which marked the syphilology of the past generation, and the fevered haste to subject the most minute lesion, untreated, to darkfield examination, which is the ideal of the present generation. Our haste is the result of an appreciation of the fact that, while the chancre is one of the first visible evidences of an already fully developed systemic infection, perhaps even with extensive involvement of the nervous system, the infection is still *unintrenched.* It is entirely conceivable, especially if the rate of reproduction of the organisms is slow, that whole areas containing the most vital structures of the body have not as yet sustained a high degree of involvement. In very early cases, spirochetes may be relatively few in the nervous system, in the parenchyma of some of the important organs, or in the vascular structures. Secondary fibrotic changes with isolation of foci by their own local inflammatory reaction have not as yet in the early case walled off foci of spirochetal reaction and made them inaccessible to spirillicidal drugs. A comparatively large number of organisms are, moreover, free in the blood-stream at the time of and just before the appearance of the primary and secondary lesions. Any measure which can be adopted to check this spirochetemia will assist in limiting the systemic dissemination of the disease by catching the organisms themselves, exposed and unprotected.

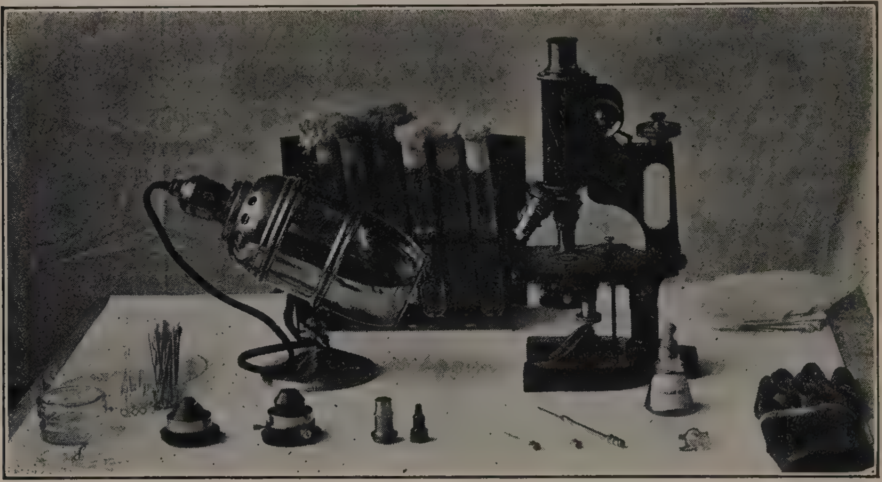

Fig 1.—The Darkfield Apparatus. This is an essential part of the equipment of every physician who treats early syphilis. Note the simplicity of the apparatus. The darkfield condenser is simply substituted for the Abbe condenser of the ordinary microscope and the stop placed in the oil immersion objective. A Welsbach gas mantle or gasoline gas lamp affords satisfactory illumination when the 100 Watt nitrogen tungsten electric lamp is not available. Early diagnosis by the finding of the Spirochæta pallida is the crux of early treatment.

There is, therefore, no more important issue in modern syphilology than that of early diagnosis of the early infection as a factor in good prognosis. While the conception of abortive cure has inevitably undergone some restriction with accumulating clinical observations of delayed secondaries and precocious tertiarism, there still remains very little doubt in the minds of experienced observers that the golden hope of treatment in syphilis is in the first few weeks and months of the disease. Even the complete establishment of a physiologic defense mechanism by waiting for secondaries does not present advantages enough to justify delay in the diagnosis and treatment of primary syphilis. No physician can, therefore, consider himself as practicing adequate modern syphilology who does not use every means for the earliest possible clinching of the diagnosis in patients who come under his care. First among these means of diagnosis is the darkfield microscope (Fig. 1) which is a relatively simple apparatus, comparatively inexpensive, remarkably accurate and effective, and in every sense of the word quite as necessary to the successful modern treatment of early and recurrent syphilis as arsphenamin and mercury. The Wassermann test repeated weekly for a month, and thereafter monthly for four months, is no less essential.

Meaning of Cure.—The worst abused term in the whole field of modern syphilology is "cure." At no point can our rationalization of the treatment of the disease more profitably begin than at this. The ordinary patient with syphilis, when presenting himself before the physician, demands a statement of the situation and the outlook. It is obvious that if the physician rashly promises the easy cure of the disease he has paved the way for risk of future disappointment, for a possible unsocial outcome through the infection of others, especially the marital partner, and for an unguarded attitude of mind which may lead both physician and patient to overlook otherwise obvious relapse. Yet if the physician fails to give the patient a definite statement, the latter, perhaps armed with the newspaper tradition of the single-dose cure by "606," seeks advice elsewhere. The situation should be placed before the patient with the utmost frankness. Certain literature published by state boards of health already does this. A definition of terms on the matter of cure is the first essential in talking to the patient. I always distinguish between clinical and pathologic cure. Clinical cure is attainable in a high proportion of cases. With the average run of patients with syphilis at all stages, I estimate that, granted full coöperation and satisfactory opportunities for observation, perhaps 85 per cent should attain "clinical cure." This term is essentially synonymous with "arrest" and I therefore carefully explain to the patient, if his case requires it, the significance of residual damage and the fact that certain changes induced by the disease are never susceptible of restoration.

The ridding of the body completely of the Spirochæta pallida is an entirely different problem from that of clinical cure. While there does not exist, as I shall presently show, any means by which we can demonstrate the occurrence of this happy consummation short of death and the microscopic examination of necropsy material, observation during the decade since the introduction of arsphenamin has gradually justified the belief that a syphilitic infection can be absolutely eradicated. This complete eradication I speak of as a "radical result." This is the restricted meaning of "cure" in early syphilis. I think it is attainable in approximately 75 per cent of the patients who present themselves in the early primary and secondary stages.

To the patient who should distinguish between the prospect of clinical cure and radical cure, the following definition of arrest may be given. The symptomatic arrest or cure of a syphilitic infection means that the patient will go through life from the completion of his treatment without further evidence of the disease and without risk of transmitting it to others. He will die of some cause other than the infection for which he had been under treatment. He will therefore be, so far as actual living is concerned, quite as if he were well. Arrest should carry with it the corollary condition of lifelong observation.

Among other terms in common use, "serologic cure" and "symptomatic cure" are by no means identical. Serologic cure means complete and permanent negativity of blood and spinal fluid. These two findings are unfortunately entirely compatible with demonstrable symptomatic progress of the disease. On the other hand, symptomatic arrest may mean the disappearance of all complaints attributable to the disease, but a persistence of serologic signs. The patient may pass through a lifetime without recurrence of any sort, but always accompanied by the serologic evidence of his infection in the form of a persistent positive blood Wassermann reaction. Whether or not symptomatic arrest with a positive spinal fluid exists, I have not yet found it possible to decide.

Determination of the Fact of Cure.—The use of therapeutic controls will be discussed more fully after the mechanism of treatment has been considered, but certain generalizations may be made here. In the first place, as in the diagnosis of syphilis, so in the question of the radical cure of syphilis no single touchstone of proof exists. To the older syphilographers the proof of cure was a long life and no complications. In many respects, with all the additions to our clinical resources made by modern laboratory methods, we have not advanced beyond this point. Time sufficient for exact determination has not yet elapsed. In fact the demonstration of the unexpected possibilities of latency, made by such studies as Warthin's, have "taken the props" from under the clinician. Radical cure now becomes a matter of faith, and a matter of faith it will remain until the complete microscopic study of the necropsy material from a sufficient number of patients radically cured demonstrates that there are no Spirochætae pallidae in their bodies. I may personally estimate 75 per cent radical cures in early syphilis and 30 to 50 per cent in latent syphilis, but these estimates cannot in the nature of things have any final value. The Wassermann reaction, far from being acceptable alone as proof of the cure of syphilis, has sunk to the level of second class evidence. It is entirely possible for an infection to pass through a physiologic gradient toward Wassermann negativity with actual progress of symptoms, merely as part of the course of the untreated disease. It is possible for the most serious lesions of the disease to develop in the vascular and nervous systems in the face of a persistent negative Wassermann reaction. The meaning of negative blood Wassermann reaction varies so much with the technic employed, as Wile has shown, for example, that it is impossible to trust it as evidence of the cure of syphilis, or even the positive reaction as evidence that the infection is active. Accordingly the practitioner is deprived of his most serviceable aid to a decision as to when to release his patient as cured. For two decades reinfection has stood as evidence that the original infection has been cured. Yet Brown and Pearce have shown that in the rabbit it is entirely possible to superpose two infections with different strains on each other in the same animal. How often such a superinfection may occur in man it is difficult to determine. But it must at least be admitted that the proof of cure of the first infection in many reported cases is the flimsiest; the alleged new infection is often quite as interpretable as a recurrence or a relapse as it is as a new infection. It seems to me that there can be only one course for the conservative clinical syphilographer to-day; that is, to refuse to accept any single test or procedure or any combination at a given time as proof of cure. Even the combination of a normal blood and a normal spinal fluid, with a negative provocative Wassermann procedure, completely negative physical examination and special examinations of the nervous system, bones and eyes, may be wrong and relapse may occur, as illustrated by the following case:

Case 1. Mrs. R. gave a history of having had a positive blood Wassermann reaction two years before. Following this discovery, she received six injections of arsphenamin and 100 intramuscular mercurial injections. She was examined October 31, 1918, and the blood found to be Wassermann negative. A provocative procedure was negative. The bone conduction was normal (eighth nerve). The eyes were normal. The neurologic examination was negative. Roentgenograms of the tibia were negative. The findings in the spinal fluid were negative. The patient was advised to be reëxamined in six months. She returned August 1, 1919. The Wassermann reaction on the blood was now strongly positive in two successive tests. There were no clinical manifestations to accompany this serologic relapse. An entirely negative result in a single, even though complete, examination is no insurance against relapse.

There is no clinical proof of cure, except, as with the older generation of syphilographers, in a long life free from complications terminating in a grossly and microscopically negative necropsy. Accordingly I feel it best to regard even the most promising early case as one for suspended judgment and lifelong observation. We can assure the patient a normal life if he will be guided by the combination of our experience and our tests. We cannot trust him, alone, to any one item or aspect of either.

In the action and reaction of modern therapeutic controversy in the syphilologic field, one notes at times a definite tendency to question whether "modern" methods of treatment have justified themselves. In an investigation of this question on my service by DesBrisay and myself, and by Barrier and myself, it became reasonably apparent, even allowing for control shortcomings in such work, that untreated syphilis runs a much less favorable course than syphilis treated by mouth or even by inadequate forms of arsphenamin and by mercury. It appeared from our study that of all the syphilitics who came under observation in the Mayo Clinic for all medical causes irrespective of syphilis less than 1 per cent had undergone spontaneous arrest. The percentage of arrest was slightly greater (6 per cent) in patients who had received small amounts of mercury and iodid by mouth, but the difference was so small that for practical purposes the two could be dealt with together. The incidence of neurosyphilis was about the same in all types, but that of the vascular, visceral, osseous, and cutaneous types was much reduced in those patients who had had even substandard modern treatment with mercury and arsphenamin. Barrier showed that the incidence of neurosyphilis was markedly higher in patients who had received no treatment than in patients who had received treatment in any form, although inadequate. For practical purposes, then, we have adopted the general rule that the aggregate prognosis of syphilis is improved by all forms of treatment, even though the securing of a maximum good prognosis in any given situation may be dependent on a highly skillful selection of the proper mode of treatment to be applied to the individual case. In other words, the prospect of a patient for securing a physiologic arrest at the onset of a syphilitic infection is so small that it pays him to assume even the risks of inadequate treatment in preference to none at all.

There is about the curability of syphilis an element of variability and uncertainty which makes predictions in individual cases impossible. Certain patients seem, from the moment their infection is established, to run an irresistibly unfavorable course. On the other hand, from a gradually growing series of observations I have felt reasonably satisfied that certain patients are probably rid of their infection within the first three or four arsphenamin injections of their first course of treatment. All subsequent treatment is then superfluous so far as they are concerned, but a rational concession toward our absolute ignorance so far as we are concerned. There does not exist any possible means of determining which patient will sustain or has sustained arrest or cure in the first few weeks of his treatment, and which patient will undergo relapse after months and years of the most strenuous therapeutic effort.

To meet the issue implied in the patient's question "Can I be cured?," let the physician explain frankly the fact that there is no absolute and final evidence of cure. Let him at least not moderate the intensity of treatment in early cases until blood and spinal fluid are repeatedly normal. *Observation* and *time* are then of the essence of the question. Most patients with syphilis can be assured of health, a long life and safety for others, by a rational system effectively pursued and combined always and above all with observation.

If the individual physician will realize that the ideal treatment of late syphilis is to treat early syphilis effectively; if he will practice and preach the gospel of early diagnosis; if he will adopt a preventive rather than a merely opportunistic or symptomatic point of view; if he will treat in accordance with a maximal instead of a minimal standard and do everything in his power to promote lifelong, complete and intelligent observation of his patient, he will have accomplished more to raise the proportion of cure in syphilis than by reams of academic argument on reinfection and the value of the Wassermann test.

THE MECHANISM OF TREATMENT

MERCURY

The average physician who endeavors to follow the literature on the treatment of syphilis will find innumerable diversities of viewpoint which will leave him in a corresponding state of perplexity if he is unable to make interpretations for himself. He would be wise to ignore the minor variations in opinion which seem so distracting, and to adhere to one reasonably successful method supported by the clinical experience of several well-known observers, and to confine himself to two or three drugs at the most. In early syphilis, system reaches its highest value, and here, under suitable control, the sailing is plainest, albeit the results of failure to observe the landmarks are often most disastrous for the patient. In late syphilis rule of thumb work is risky, and here a thorough knowledge of just what the therapeutic implements employed will do is of the utmost importance. Such energy as the practitioner devotes to variations is best concentrated on the individual late case.

To treat syphilis successfully, one must believe thoroughly in the value and effectiveness of treatment. Half-hearted acceptance of arsphenamin, because every one is using it or talking about it, is the predecessor of inefficient use. Encouraging results are the rule and not the exception in a properly inspired technic, and the patient should be given the benefit of the energy which this knowledge puts into his treatment. On the other hand, only the untrained and inexperienced optimist expects or offers guarantees.

Certain general knowledge concerning modern methods of treatment assists in interpreting the literature and current opinion. The discovery of the Spirochæta pallida has made it possible to watch the actual effect of our medicaments upon the cause of syphilis. Judgments of the effectiveness of a spirillicidal form of treatment should be based on the actual disappearance of the organisms from the lesions within a known maximum time. Any physician with a darkfield can satisfy himself whether or not in an early case his medication is effective, by watching the disappearance of spirochetes precisely as gonococci are watched and counted in gonorrhea. In syphilis it is important to remember that the healing of a lesion is not a demonstration of the effectiveness of a drug in destroying the organisms. The whole effect may be merely an involution of the granuloma, leaving the organisms little affected. The claim of manufacturers or physicians that their preparations or technic causes involution of lesions is, therefore, merely a return to the limitations of the symptomatic age. It is important to recall too that the action of a drug in vitro and in vivo may be entirely different. For example, the mercury ion is a powerful germicide in direct contact with spirochetes in a test tube. If a protein is present, there is a relative protection. In the body this protection is so marked that the drug becomes a disappointment as a spirillicide, and therapeutic plans which use mercury as a direct spirillicide become unsound. Still another consideration which must be borne in mind is the fact that toxicity and therapeutic efficiency do not mean the same thing, and that a preparation of a very low toxicity may be correspondingly ineffective therapeutically. In the case of the arsphenamins, there is evidence to support this contention. The claims of originators or marketers of therapeutic ideas and preparations for the treatment of syphilis must be examined from this viewpoint before they are accepted.

The threatened displacement of the therapeutic use of mercury in syphilis by the spirillicidal era has not materialized. It therefore behooves the physician to devote as much thought to the rational application of this drug to syphilis as to the use of the more spectacular arsphenamins. In fact, as the first in point of time, the drug deserves first consideration in discussing the mechanism of treatment. Modern investigation has thrown much light on its action, the essential points of which may be summarized as follows:

Mercury is a builder of tissue resistance to the Spirochæta pallida. Paradoxically speaking, this most specific of drugs has the least direct specific action on the cause of syphilis. The Spirochæta pallida can thrive in a concentration of mercury in blood-serum in the test tube which is two and one-half times as great as the maximal concentration of the drug in the blood-stream when the patient has reached the physiologic saturation point and toxic effects appear. In just what way the resistance-building action is exerted it is as yet difficult to say, but it would seem to be cellular. While mercury has undoubted spirillicidal effects, they are very low in proportion to its toxicity, so that the use of this drug for spirillicidal action per se is no longer justifiable in view of the great superiority of the arsphenamins. Rubin and Szentkiralyi make an effective comparison of neo-arsphenamin and mercury on this point by showing that 3 dg. of neo-arsphenamin destroys the spirochetes in a superficial lesion within twenty-four hours, while after five injections of mercury salicylate in twenty-seven days the organisms were still demonstrable in the partially healed lesions, although their viability was markedly reduced. This evidence of the low spirillicidal efficiency of mercury can be borne out by any considerable clinical experience. Even under inunctions or large doses of mercury salicylate, it is entirely possible for active spirochete-containing lesions to develop on the mucous membranes and around the anus. The question as to whether these are produced by a resistant strain of organism not susceptible to the action of mercury, or arise from a peculiarity of the patient which renders him incapable of response to the resistance-stimulating action of mercury, is not fully settled. Fantl's recent suggestion that mercury may increase spirochetal resistance seems not to have been borne out. Experimentally speaking, there is evidence that the Spirochæta pallida can acquire resistance to mercury in the medium in which it grows, and that it can lose that resistance when the mercury is for a time removed. If the principle established by this work can be transferred bodily to the infected patient, it affords a completely satisfactory explanation for the effect of the rest interval and of intermittent treatment in the management of the disease. While the patient is not taking mercury, his spirochetes are losing their resistance to the drug and become susceptible to another assault, which is the more successful because of the rest period.

Mercury causes a reversal of the positive Wassermann reaction to negative, although the exact mechanism of this action must await better comprehension of the Wassermann reaction itself. Mercury, if intensively given, is if anything somewhat more effective than the arsphenamins on this score.

While mercury is a builder of resistance to the Spirochæta pallida, it is by no means necessarily a builder of general resistance or constitutional good health. While its effect on constitutional debility due to syphilis at times creates the impression of a tonic action because of its effect on the infection, the actual physiologic effect is in the main depressant, especially in vigorous dosage. This action, in contrast with other specifics such as quinin, to some extent limits the usefulness of the drug and the technic of its application. The depressant effect of mercury extends beyond merely general reactions, and, as shown by the work of

Toyama and Kolmer, for example, affects immune body formation, which is less under very large than under moderate dosage. It should be borne in mind, then, that knowledge of the therapeutic action of mercury does not justify the belief that the more used the better. The resistance of the patient should be built up to the highest point, not needlessly depressed by overstrenuous therapeutic use of the drug. The resistance sought is specific, to be gained only by sufficient dosage, and not the mere gain in weight that may result from the use of mercury by mouth as an intestinal antiseptic.

Pharmacologically speaking, mercury circulates in the blood in a protein combination. The concentration of this combination remains fairly constant under effective administration, and is spoken of as the saturation point for the drug. The administration of amounts in excess of those required to maintain saturation gives rise to toxic symptoms. The elimination of the drug takes place through the gastro-intestinal tract and the kidneys. The effectiveness of various mercurial preparations varies not only with the dosage in which they are administered, but with the rate at which they are absorbed. Some of the more complex molecules, such as those of the recently popularized insoluble salts, are less effective than some of the older preparations probably for this reason. A soluble salt is rapidly absorbed and has a rapid effect on the organisms. An insoluble salt is slowly absorbed, and has a correspondingly lower spirillicidal power.

The toxicity of the mercurial ion for the kidneys and the gastro-intestinal tract is thus far the chief clinical application of the known pharmacology of the drug. It appears from recent studies that it has also a pronounced toxic effect on the heart and on the vascular system, but this action, so far as I have been able to detect clinically, comes on so much later than the other effects observed that in ordinary treatment it plays only a small part. On the other hand, it must be distinctly stated that there is room for debate on this matter and that the influence of mercury in producing chronic arteriosclerotic changes has not yet been worked out. The production of anemia by the hemolytic action of the drug is, of course, familiar, but again, except through poor management, this effect is now rarely observed on the average patient, relieved as he is by the use of hematopoietic stimulants such as the arsenicals.

The function of mercury in treatment is, then, fairly well defined. As a resistance builder, it should be employed in all cases in which the patient is expected to wear out his infection, rather than abolish it at a single blow. Inasmuch as the wearing-out process is probably a factor in at least 60 per cent of all recoveries, and 90 per cent of all symptomatic good results, the vital place of the drug in treatment is not open to dispute. On the other hand, mercury has definitely and sharply defined limitations. It does not control infectiousness with even a small fraction of the effectiveness of arsphenamin. It is a depressant and, if pushed vigorously, uses up the patient, while it may or may not control the disease. It is hard on the kidneys and sometimes cannot be employed to full effectiveness because of this limitation.

Modes of Administration of Mercury.—Three and perhaps four methods of administering mercury deserve the confidence of the practicing physician. A certain never-ending enthusiasm for the revival of antiquated procedures, such as fumigation and rectal suppositories, must be deprecated as superfluous and as interfering with an intelligent concentration on the proper use and control of the standard procedures. The four accepted modes of administering mercury are by mouth, by inunction, by the injection of mercurial salts intramuscularly, and of soluble mercurial salts intravenously.

By Mouth.—This method is the traditional earmark of the French school. Its usefulness is distinctly limited, in the estimation of the more vigorous modern therapists, to symptomatic action on trivial syphilis. Certainly from the biochemical and bacteriologic standpoint it is the least intensive of all modes of administering mercury. It is exceedingly difficult to attain the saturation point for the blood by this method of administration, although it is easy enough to produce the symptoms of pseudosaturation in the form of gastro-intestinal reaction and salivation. It may be used for persons with benign long-standing syphilis of the last two decades of life, and for younger persons merely as an occasional interim treatment, or as an aid to the rapid induction of saturation by the slower but more intensive method of inunctions. It is valuable in the management of patients who present conditions that cannot stand the shock of rapid healing, such as lesions of the heart and liver. It is sometimes useful in the face of temporary contra-indications, such as the limited renal tolerance of pregnancy. *It has no place whatever in modern conceptions of the treatment of early syphilis.* The physician who thus employs it is frankly placing his patients largely on their own resistance mechanism, and, if he uses it in combination with arsphenamin, is directly inviting all the forms of relapse and premature allergy and all the indefinite prolongation of infectiousness which have marked the misapplications of the first decade of modern treatment.

Jonathan Hutchinson's favorite preparation, mercury with chalk, is in my experience the most satisfactory mercurial for oral administration. The dose is from 1 to 3 gr. three times a day. The bichlorid, 1/12 gr. in peppermint water well diluted three times a day, is also satisfactory although more irritant.

By Inunction.—Mercury applied in the form of an ointment came into use as early as 1497, various preparations being proposed by Berengario de Carpi and Jean de Vigo. Astruc mentions the inunction, but it apparently underwent an eclipse as a result of excesses in dosage and the introduction of guaiac from Haiti during the early years of the sixteenth century. By 1564, however, Fracanziana mentions that the ablest physicians had again found it necessary to resort to inunction.

The method has now the endorsement of the ablest syphilographers of the world, and is generally admitted to be the most trustworthy of the more intensive methods of administering mercury. The limitations placed on its usefulness by insufficient dosage, by the possibility of betrayal, by its messiness, and by its tendency to irritate the skin, have given the average physician plausible excuse for underrating and underusing the method. The pea-sized inunction of the past generation belongs with the birdshot protiodid pill in a museum of syphilologic antiquities. Personally I was convinced, in watching the practice of the late Frederick G. Harris, that ability to make patients employ the inunction effectively is to no small degree a matter of personality. To keep a patient on inunctions for a full three years of treatment is a test of one's grasp of the art of syphilology as distinguished from the science. Instead of depreciating the "rub" and apologizing for it, the average physician should magnify it, glorify it, give it a mechanism, and stand to his guns on the necessity for its employment. In this way he will secure effective treatment for a surprisingly large proportion of his patients.

The special advantages of mercury by inunction include absence of cumulative effect. Two baths and a sweat will to a large degree remove the patient from the influence of the drug. Dosage, while not exactly measurable, is none the less effective by a good technic. Hoffman has suggested that there is some stimulation of the "esophylactic" or protective function of the skin by the rubbing. No method is less injurious to the kidneys in proportion to its effectiveness, and none better tolerated by the gastro-intestinal tract. Salivation can be controlled by careful mouth prophylaxis, with the maintainance of an effective dosage. The disadvantages of the inunction are the tendency to induce irritation of the skin in susceptible persons, and a rather slow attainment of physiologic saturation with mercury. This can be hastened by a week or two of coincident oral medication. It should be borne in mind that less than two weeks of inunctions has negligible therapeutic effect.

High points in the use of inunctions include a measured dose, not less than 4 gm. equivalent to 30 gr. metallic mercury (the official unguentum hydrargyri, which is 50 per cent metallic mercury). I have found the suspension of mercury in cocoa butter very satisfactory, and this preparation rubs sufficiently dry to be less vexatious than inunctions with softer bases. Prepare the skin with soap, water and alcohol. Use six sites for the rubbing each week, in rotation, avoiding hairy spots. The upper and lower flanks and the insides of the thighs or the back are satisfactory, the latter, especially, if assistance can be had. Rubbing should be done for twenty minutes by the clock with moderate energy. Overdoing induces irritation. The patient should keep the ointment out of the flexures, wear the same underwear night and day, take a hot bath only once a week, at which time he should thoroughly cleanse and powder himself. He should then resume rubs the next night. A cold shower without soap or rubbing may be taken more frequently in hot weather. Inunctions should be prescribed in courses of forty to eighty.

The absorption of mercury by this method is largely through the skin, though experimental work shows that the respiratory tract may be an avenue if the drug is left on the skin. Cole has proposed a so-called "clean inunction" in which longer rubbing (thirty minutes) has been made to take the place of the respiratory absorption of the volatilized excess, which may be wiped off as soon as the rubbing is finished, instead of collecting on the underwear. The excess is removed from the skin with benzin after thirty minutes rubbing. I have not as yet been able to evaluate my experience with the method, but Cole's results were well controlled.

The attempt to substitute calomel for metallic mercury in the inunction, while praiseworthy, has not met with the general acceptance of syphilologists, and several, including myself, who have tried it, have abandoned it. While mercury is absorbed, the action seems to be much less effective than that of the metallic rub.

By Intramuscular Injection.—This method of administering the drug is the earmark of the German school and is easily the most intensive of those commonly used. It is intensive enough for practically all treatment which the average physician should attempt, and in fact will even then be employed at times with more enthusiasm than judgment.

The results and technic of administration of mercurial salts intramuscularly are dependent to a large extent on the salt employed. Two types, the soluble and insoluble, are in common use. Among the former are the bichlorid, the succinimid, the red mercuric iodid and the benzoate. Among the latter are calomel, mercuric salicylate and suspended metallic mercury in the form of the gray oil. The insoluble preparations are suspended in fatty bases.

Soluble salts are rapid in action and transient in effect, dose by dose. They are, therefore, relatively not cumulative. Their quick absorption makes for vigorous action, and I have repeatedly seen cases resume favorable progress which had come to a standstill under treatment with insoluble salts. Lier pointed out that the control of infectious recurrences appearing during the use of an insoluble salt could be accomplished by substituting a soluble salt for a few injections. These advantages all appeal to me as of the highest importance in treatment, and as overbalancing the greater convenience of the insoluble salts whenever the use of a soluble salt is at all possible. Soluble salts must be given daily or at least as often as from three to five times weekly, while insolubles may be given once in five to seven days, a matter of convenience to some patients. The irritation of a soluble mercurial injection by a good technic is somewhat more acute but shorter-lived than that of an insoluble salt, but I have found this no drawback in thousands of injections.

In considering the therapeutic use of the insoluble mercurial salts which are usually given in oil suspension, the rate of absorption is of the greatest importance. The impression that, because a substance is injected it is absorbed, and that the dosage is, therefore, definite, is erroneous in this case. The absorption of insoluble salts is very slow, and a rapid accumulation occurs, under any system of dosage, which leaves the physician altogether at sea as to how much mercury his patient is getting or will get. Cole showed that mercury salicylate is apparently the most rapidly absorbed of the insoluble salts, to judge by the Roentgen ray, and that the gray oil, long popular among German-trained syphilographers, is absorbed with such extreme slowness that it cannot be regarded as other than dangerous. If this defect of insoluble salts is taken into account, it can, of course, be transformed into a virtue. Whenever a patient needs a depot for the prolonged absorption of mercury, an insoluble salt should be used. Thus it makes a good tapering-off of an intensive course, or of treatment for those who are for long periods out of reach of a physician. But the repetition of course after course of an insoluble mercurial, or even the use of an insoluble early in an ordinary course, has in my experience been therapeutically less effective and paves the way for recurrences which do not happen so readily under inunctions and injections of soluble mercurials. A species of compromise in the use of a soluble salt in an insoluble manner is the use of the bichlorid in oil, 1 to 2 gr. a week.

Whenever possible, then, I believe that a soluble salt should be used intramuscularly. The dosage of the bichlorid is $\frac{1}{6}$ gr. daily, of the succinimid, $\frac{1}{6}$ to $\frac{1}{4}$ gr. daily. Both solutions may be made up in 30 c.c. quantities with the proper dose in 1 c.c. of distilled water and kept in a dark bottle. They are self-sterilizing. Great care should be taken to assure the chemical purity of the salts, or they may be very irritating.

If an insoluble salt is to be used, the salicylate should have preference. A 40 per cent suspension in lanolin and olive oil[1] may be used, but dilution of this formula to 10 per cent often causes less irritation. The dose is from 1 to 2 gr. a week. Doses of 3 gr. may be given, and doses of 1 gr. are insufficient for regular use in the adult. The ready-prepared preparations on the market in ampule form should be made up in vegetable oil, for it has been definitely shown that the use of paraffin oil as a base may lead to the formation of foreign body tumors. Even this precaution does not wholly protect.

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[1]	℞	Hydrarg. salicylat.	6
		Lanolini	1
		Ol. olivæ (sterile) q.s. ad	15

M. Sig.: For intramuscular; shake well.

Technic of Intramuscular Injection.—The technic of intramuscular injection is a matter of considerable moment. The unsatisfactory results obtained by the general practitioner and his difficulty in holding patients to treatment are not infrequently due to lack of technical expertness rather than to any intrinsic quality of the drugs employed. The first essential for a successful intramuscular injection is a satisfactory needle and syringe. The ordinary all-glass 2 c.c. Luer syringe is satisfactory for all purposes. The needle should be either steel or tempered gold, twenty-two gage, 1½, 2, or 2½ inches in length, depending on the thickness of the fatty panniculus of the buttock. With a needle of this gage, it is essential to use the aspiration technic described in detecting the presence of the needle point in a vein. The advantage of the smaller needle lies in the prevention of infiltration and leakage. The needle point should have a long bevel and be very sharp. It is easily possible to turn the point of such a needle by contact with hard substances, including the bottom of the bottle. The introduction of a "turned" needle may be very painful. The turned point can be detected by a grating feeling when the needle is wiped with a cotton pledget before injection.

Needles must be watched for signs of pitting, rusting or corrosion, and after use should invariably be carefully washed with alcohol or ether to dry them. Steel needles used with a corrosive solution, such as bichlorid, must be especially often examined. Breakage of the needle is an exceedingly unpleasant accident and can be avoided only by careful attention to both needle and technic. Test the needle from time to time by a forcible attempt to bend the shaft on the hub.

The needle and syringe can be sterilized by thorough rinsing in alcohol, or by boiling. If alcohol is used, it should be carefully and completely expelled and the needle thoroughly wiped before it is introduced.

Injections may be given with the patient standing or lying down, preferably the latter. Women should remove their corsets. Have the patient relax by turning the head away from the operator and dropping the arms over the side of the table. A better relaxation of the buttock can be assured by having the patient toe in instead of out. Fill the syringe and the needle completely with the requisite amount of the solution or suspension by aspirating through the needle.

The buttocks should be used in alternation. The point of injection should be in the upper outer quadrant of the buttock, near the center. If lower than this, the injected mass will find its way to points where the weight rests in sitting, and will cause corresponding discomfort. Injections may be made nearer the sacrum, but in my experience there is somewhat more risk of striking bone and of causing an infiltration around nerve roots, resulting in obstinate sciatica.

Cleanse the site of injection vigorously with a cotton pledget wet with alcohol. Grasp the syringe in the right hand between the thumb and the index, middle and ring fingers, with the piston resting against the index finger so as to prevent its slipping downward from its own weight and expelling a portion of the solution along the needle track. With the left hand, press downward firmly on the tissues of the buttock, drawing the entire panniculus downward toward the heel. Introduce the needle with a single, quick stroke to its full length, inclining it slightly downward and inward. As soon as the needle is introduced, release the left hand and, while still steadying the syringe with the right hand, pull upward on the syringe piston with the left. This is the process of aspiration which is in my experience the most reliable means of detecting leakage of blood from the capillary or vein. It is preferable to detaching the syringe or using an empty needle, especially with a small caliber needle. If no tinge of blood can be obtained after ten seconds aspiration, the dose may be injected slowly and gently. If the needle is properly placed the injection will require very little effort. The needle should not feel as if stuck rigidly in a board. As soon as the injection is completed, place the left hand again upon the buttock, drawing downward as before the injection. Remove the needle with a quick pull of the right hand and at the same instant quickly slide the buttock upward without pressure, so as to secure a valve action on the needle track. With a little practice the injected material can be confined entirely to the fascial region and leakage into the subcutaneous tissue entirely prevented. Immediately massage the site of injection lightly with the cotton pledget used in cleansing the surface of the skin.

Certain additional details are of importance. Superficial infiltration of hazelnut to hickory-nut size in the fat or subcutaneous tissue usually results from leakage along the track of the needle, or from imperfect wiping of the needle before the injection is made. To avoid such infiltration, secure the patient's complete relaxation by the position described and by talking with him reassuringly before introduction of the needle. Use a small caliber needle and completely empty the syringe. In withdrawing remove the needle rapidly and employ the valve technic described. Deep, painful, lemon or orange-sized infiltration may result from too deep an injection, either into the body of the muscle or close to the periosteum. Pain down the leg lasting for any considerable time usually means that the mass is producing infiltration about the sciatic nerve.

When circumstances permit the patient to give attention to the matter, it is an excellent plan to advise the application of hot towels or a hot-water bag to the site of injection for two or three hours, or for the night following the injection. This may be done even though the patient experiences no discomfort, because it seems to diminish the tendency to slowly progressive fibrosis and thickening of the injected tissues which occurs to some degree in all cases in which intramuscular methods of treatment are used over a long period of time.

Complications of Intramuscular Injection.—The complications of intramuscular injection are: (1) breaking the needle; (2) aspiration of blood; (3) embolism; (4) pain; (5) induration; (6) abscess; and (7) sudden onset of salivation and nephritis.

Breaking the needle may result from defects in the needle, from striking bone, or from a sudden movement of the patient. Precaution should be taken routinely to guard against the last point, especially in children. If the needle breaks, maintain absolute silence, keep the left hand in position with the buttock drawn down, and attempt to recover the needle with a hemostat through a small incision. If the buttock is released, the needle is lost and Roentgen-ray examination and operation are required to recover it. If the smallest trace of blood appears in the solution of emulsion in the syringe during aspiration, the needle must be immediately withdrawn and reintroduced at least 1 cm. from the original site of injection. To continue the injection in the face of leakage of blood may mean death from embolism. Embolism should be a rare occurrence if the technic described is used. I have seen only two such cases, both before I adopted the aspiration technic. The symptoms are cough on arising from the table, with occasional pain in the side. At times definite pneumonic or pleural symptoms develop within the ensuing twenty-four hours as evidence of infarction. Cerebral embolism is exceedingly rare, but fatal.

Pain at the site of the injection varies with different patients. Those who have sufficiently prolonged or severe pain should not be treated by this method, but the practitioner should nevertheless not be too readily discouraged by a complaining attitude on the part of the patient. If the discomfort lasts only a short time, say from two to six hours, it may be regarded as negligible. Hot applications and massage or painting with tincture of iodin may give relief.

While indurations are occasionally unavoidable in obese patients, their common occurrence is evidence of either an unusually irritating quality of the drug or an unsatisfactory technic. Superficial induration means leakage; deep induration means too long a needle or its improper placing.

Abscess should be exceedingly rare. I have seen 2 cases in 70,000 injections. The abscess is usually sterile and resolves on drainage. Some softening may occur in indurations which later subside under heat and counterirritation.

Sudden onset of salivation and nephritis may be a complication especially of insoluble intramuscular treatment. It is due to sudden absorption of encapsulated mercury in infiltrates and nodules. In view of the fact that the insoluble salts of mercury are cumulative in their action, their use should be discontinued if the formation of nodules and infiltrates is unavoidable. Heat and massage assist in the resolution of such accumulations in the tissue.

An important point in the injection of insoluble salts is to be sure that the emulsion is homogenous and that all of the solid material is completely suspended. A good test for this is to shake the bottle or container until no more solid material can be recognized in the line of juncture between the side and the bottom of the bottle. The container should be shaken again before each injection, or the last of a series of patients will receive more mercury than oil.

By Intravenous Injection.—Intravenous mercurialization has obtained a measure of acceptance during the past several years. Personally I have never felt the need of employing mercury intravenously because it seems possible to secure all the effects which one should reasonably expect from the drug by the intramuscular use of a soluble salt. The risk of venous thrombosis and of acute mercurial nephritis, while much reduced by improvements in technic, is still present. The drugs of election are the oxycyanid and the bichlorid.

The technic of intravenous injection of mercury bichlorid given by Conrad and McCann is substantially as follows: The dose ranges from 0.6 to 2 c.c. of a 1 per cent solution of mercuric chlorid in physiologic sodium chlorid solution. The dose is increased 0.1 c.c. at each injection, and the injections are given twice weekly. The mercurial solution is drawn into a 10 c.c. all-glass syringe through a 22-gage platinum needle. The needle is then introduced into the vein by the usual technic, and 8 to 10 c.c. of blood drawn into the syringe. This is mixed with the bichlorid solution by rotating the syringe and needle without removing the needle from the vein. One-half of the mixture is then injected, and another 8 c.c. of blood drawn into the syringe. The entire content of the syringe is then finally injected into the vein. The formation of a mercurial albuminate in the syringe before injection prevents thrombosis. It is important to be sure that the needle is free in the lumen of the vein and that the bichlorid and blood are completely mixed in the syringe before injection.

A number of bizarre methods of administering mercurial preparations have periodic revivals, such as fumigation, a method which ever since the recognition of syphilis in Europe has been tried and has failed repeatedly. Suppositories have no advantages whatever and no excuse for existence. Various special preparations of mercury embodying the colloidal form of the drug have been suggested, but their special advantages are not as yet apparent.

COMPLICATIONS OF MERCURIAL TREATMENT.—The chief untoward effects of mercury appear in the kidneys, the gastro-intestinal tract, the blood, the skin, and in the production of asthenia, often associated with arthritis.

Irritation of the Kidneys.—Under properly conducted treatment, irritation of the kidneys should be the first important sign of unfavorable reaction. It can only be detected, short of marked injury, by systematic examination of the urine. This must be both chemical and microscopic, for the former detects only the later signs of injury. Mercury produces nephrosis. The order of the appearance of urinary signs is polyuria, casts, albumin, and red blood-cells. The first three, while signs of irritation, do not necessarily demand cessation of treatment unless continuous and pronounced. The permanent presence of any considerable amount of microscopic blood is a sign of renal injury and should cause the temporary or perhaps permanent suspension of intensive mercurialization. Occasional showers of casts are not especially significant, and nearly all patients show them under mercury.

Alkalinization with sodium citrate may protect the kidney to some extent, though just how much it is difficult to determine. The removal of foci of infection, especially from the mouth, may markedly increase the tolerance of the drug. Certain patients under mercurial treatment gain in tolerance, others gradually lose, without any apparent reason for either change.

Mercurial Stomatitis.—The stomatitis produced by mercury is apparently due to an infection with saprophytic organisms which produce hydrogen sulphid. This, in combination with mercury in the tissues, causes necrosis and a further stimulation of the saprophytic infection. The logical prophylaxis and treatment is, therefore, a thorough cleaning up of the mouth and throat with removal or treatment of infected or carious teeth, pyorrhea and gum pockets, this to be done, if possible, before treatment has been carried to the point where symptoms are likely to appear.

Treatment initiated too suddenly, as by a heavy dose of mercury salicylate intramuscularly, may result in an abrupt onset of obstinate salivation which may greatly delay and hamper further treatment. Every patient who is placed on mercurial treatment should carry out the following régime: (1) brush the teeth three times a day with an alkaline oxidizing tooth paste; (2) paint the gums twice a day with an astringent mixture of 1 part tincture of kino and 2 parts tincture of myrrh; and (3) avoid acid foods.

If signs of tenderness or discomfort on clenching the teeth appear, dilute hydrogen peroxid may be used occasionally during the day as a mouth wash. Proper dental attention will often arrest beginning salivation.

Once a stomatitis is established, every effort should be made to stop the absorption of mercury. It is the impossibility of doing this which makes the reaction to insoluble mercurial salts given intramuscularly so obstinate at times. On the other hand, it is entirely possible in even a fairly severe case, with proper dental attention, to clear up a salivation of moderate grade. No extractions should, however, be attempted until the patient recovers. If the case is severe, the disturbance of nutrition may be serious and the patient should be put to bed. The mucous membrane of the cheeks should be separated from the gums, and the tongue from the gums by thin strips of cotton soaked in boric acid solution. Dobell's solution will relieve the discomfort to some extent. One-fourth to ½ of 1 per cent zinc chlorid in liquor antisepticus alkalinus N.F. may be markedly beneficial. Dilute potassium permanganate may be used, but is unpleasant and discolors the teeth.

Extreme grades of stomatitis may be accompanied by alarming loss in weight and rapidly progressive asthenia which demands the utmost effort to maintain the patient's nutrition. A full soft, high carbohydrate diet and alkali by mouth are important.

An obstinate tendency to stomatitis is, of course, a serious handicap to treatment. On the other hand, the inclination of the physician too often is to stop mercury when mouth symptoms appear, rather than to insist on a rigorous prophylaxis in order that mercurialization may be continued. It is perhaps needless to say, at the present day, that the induction of salivation is in no sense evidence of the effectiveness of the treatment, or an end to be sought.

Gastro-intestinal Irritation.—This group of complications, most common with mouth treatment and most serious and disturbing in the form of a bloody diarrhea following an intramuscular injection, is controllable by giving the drug well diluted before or with and not after meals, and by attention to diet. A bland, rather soft diet, without the residue-producing foods or fruits, is essential. The patient should be warned against self-medication for cathartic purposes. The constipation of mercurialization may be relieved by paraffin oil, bran or agar, rather than by fruits and laxatives. The acute attack of diarrhea calls for bismuth and charcoal, and paregoric, with an ice-bag to the pit of the stomach, or turpentine stupes.

Anemia.—The combined use of mercury and arsphenamin has made the anemia of mercurialization relatively rare. Most of the cases seem to occur in hospitalized patients and especially in children. The blood changes are of the secondary type and respond readily to good hygiene and the use of Blaud's pill. For the patient who has at the outset a severe grade of anemia from some cause other than syphilis, considerable caution is necessary in the use of mercury and it is well to postpone it until transfusions and arsphenamin have brought the hemoglobin up to 50 or 60 per cent. The tolerance may then be tested by mouth medication before inunctions are begun.

Mercurial Asthenia and Arthritis.—Loss of weight, a pasty pallor, mental depression and anxiety, anorexia and gastric disturbances, with vague pains in joints and muscles amounting to actual arthritis in severe cases, constitute the symptoms of constitutional intolerance on overtreatment with mercury. Individual susceptibility and even the state of mind seem to predispose. The arthritic phase is apt to be uppermost in those who cannot tolerate inunctions, and with a mild degree of chronic stomatitis they may run a low fever and be so crippled with "rheumatism" that the treatment must be abandoned. A careful cleaning up of foci of infection, with a general hygienic régime, may increase the tolerance of such patients. Urinary retention may often produce a picture of this type under vigorous mercurialization. The overprolonged use of intramuscular treatment with cumulative insoluble salts may also be responsible. A complete rest and a change of scene may be of benefit.

Cutaneous Irritation.—Explosions of exfoliative dermatitis have been known to follow a single intramuscular injection of a mercurial salt. Patients whose skins have once reacted to arsphenamin, or who have a history of dermatitis, may be particularly predisposed. Inunctions, when rubbed in too vigorously or in patients who have seborrheic skins or marked focal infections, may give rise to a dermatitis beginning in the flexures and extending over the whole body. So marked is this tendency that I have practically abandoned the simultaneous use of the inunction in patients receiving arsphenamin. Prompt removal of the mercury from the skin, with the use of a bland lotion such as calamine lotion, several oatmeal and soda baths, and Lassar's paste without salicylic acid, or olive oil and limewater, will arrest the average case of beginning "rub dermatitis"; but the rubs should not be resumed for a number of weeks after all infections are cleaned up, if at all.

Bismuth

The use of bismuth in the treatment of syphilis may be mentioned in connection with that of mercury, which it closely resembles in action. The drug was studied and experimented on by Sazerak and Levaditi in the form of sodium-potassium-tartro-bismuthate. It has had an extensive though brief trial in France, and is now marketed in the form of aqueous and oil suspension. The drug produces a fairly rapid disappearance of spirochetes from lesions comparable to that of mercury intramuscularly, and affects the Wassermann reaction in much the same way. The complications, which occur in as high as 40 per cent of cases, are rather trying and consist of the appearance of bismuth pigmentation of the mucous membranes of the mouth, and stomatitis. Sudden death may follow the entrance of the smallest amount into the blood-stream. The drug is not given by mouth. As yet, judgment as to the value of this preparation in syphilis must be suspended, but present indications are that, while it may occasionally be beneficial for patients who appear to be mercury-fast, it has no striking advantages over mercury, and some distinct disadvantages in the ordinary treatment of the disease.[2]

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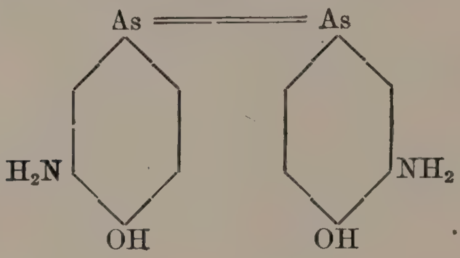
[2] Current reports of the action of bismuth salts in syphilis are increasingly favorable.—Author.

THE ARSPHENAMINS

The arsenical phase of modern syphilotherapy revolves around the various derivatives of the arsenobenzol base whose formula is:



Following the terminology adopted by the United States Government during the War, these compounds may be designated "arsphenamins." They include such derivatives as arsphenamin proper, or "606" (dihydroxy-diamino-arsenobenzol dihydrochlorid); neo-arsphenamin, or "914," whose composition is somewhat variable; and various other preparations, such as sodium arsphenamin, silver arsphenamin, neo-silver-arsphenamin, sulpharsphenamin, and so forth. The designation "arsphenamins" will be used throughout this description to avoid the employment of proprietary names designating products of individual manufacturers, such as salvarsan, diarsenol, arsenobenzol, and kharsivan.

Arsphenamin and neo-arsphenamin have demonstrated their value in the treatment of syphilis, and their use will be discussed in detail. The subsequent modifications have not as yet demonstrated any distinctive advantages. Discussion of their technic and of the controversial claims of the literature merely confuses the situation for the average physician and is therefore omitted.

The first principle to bear in mind concerning the use of the arsphenamins is that their action is spirillicidal primarily, and only secondarily resistance-building. They are thus the logical complements of mercury, the principal action of which is resistance-building, and which is only indirectly spirillicidal. The rapidity of action of the arsphenamins on the Spirochæta pallida is remarkable. Half the ordinary therapeutic dose of an effective neo-arsphenamin destroys all the organisms in a surface lesion within from eight to twenty-four hours. The influence of the drug in the control of infectiousness is therefore incomparably superior to mercury. Relapse will, of course, occur, for the drug, unfortunately, does not act with such spectacular effect on all foci of the infection. It is, however, entirely possible in rare cases for a single large dose to produce what appears to be a complete sterilization of a fresh infection. This occurrence is so rare, however, that it must form no part of rational therapeutic calculations. It is the repeated action of a series of doses which cures, if cure is possible.

Just as a tolerance to mercury on the part of the Spirochæta pallida can be demonstrated in cultures, so a similar tolerance to arsphenamin can be developed and will wear off if the organisms are again grown in an arsphenamin free medium for a time. There exists, therefore, the same reason for rest intervals between courses of arsphenamin treatment, which exists in the case of mercury. There is, moreover the same suggestion of the possibility of arsenic fastness to correspond to a supposed mercury fastness.

Arsphenamin, by any effective mode of administration, is, like the insoluble mercurial salts, cumulative in its action. While the mechanism of elimination is not completely worked out, there is a definite storage of arsenic from the drug in certain depots in the body. This is of course not the same as a storage of arsphenamin as such, but it gives rise to the late effects of arsphenamin, both good and bad, which resemble those of arsenic. The structures which serve as storage depots are the liver chiefly, then the spleen, the skin and the intestinal mucosa. Elimination takes place to the extent of about 25 per cent by way of the kidneys, and about 75 per cent by way of the intestines, a fact which is of importance in the after-care of patients treated with arsphenamin. The rate of elimination increases with the rate of administration. The drug has relatively much less irritating effect on the kidneys than has mercury (about one-fiftieth, according to Schamberg, Kolmer and Raiziss). On the other hand, clinically, and in part at least experimentally, the arsphenamins affect the vascular system and the blood much more than mercury.

Not all the action of the arsphenamins is spirillicidal. The resistance-building qualities of the drug, while not nearly so specific for the Spirochæta pallida as those of mercury, have a marked influence on the course of a number of diseases, including syphilis. This tonic action, in contrast to the depressant effect of mercury, is an invaluable aid in offsetting the defects of mercury. Non-specific effects in the use of the arsphenamins are secured by small or moderate rather than by large doses. It is apparent that there is a certain conflict possible between the direct spirillicidal action of the drug and its slower immunity-building power. It becomes necessary to decide, therefore, in the use of the arsphenamins in any specific type of syphilis, which effect is desired. Not only do large doses fail to produce resistance, but there is reason to suspect from the work of Toyama and Kolmer that they actually reduce it, an action long suspected on clinical grounds.

In planning the therapeutic application of the arsphenamins, a point spoken of under the discussion of the physiologic defense mechanism must also be borne in mind. A drug which destroys the organisms which are the source of the defense reaction on the part of the tissues, if it does so rapidly enough, leaves the body without its physiologic protection. It is precisely this that the arsphenamins are suspected of doing in early syphilis, and it is this property or rather lack of property which makes it so essential to combine an effective mercurialization with every formula for the use of arsphenamin in syphilis. "Combined treatment" is therefore rarely a matter for option or discussion. From our present knowledge, it is a logical necessity. From the foregoing considerations we can, then, evolve a theory of arsphenamin dosage somewhat as follows:

If spirillicidal effects are sought, use large doses at short intervals so as to keep the body saturated with the drug.

If resistance-building is sought together with a moderate spirillicidal effect, use small doses at longer intervals.

If both effects are desired, give several large initial doses, then drop to smaller doses at longer intervals.

Since the drug is cumulative in respect to complications, it should not be too long continued for spirillicidal effect.

Do not depend on arsphenamin alone for the resistance needed to control syphilis, especially in its early stages. The resistance-building effects are neither marked enough nor specific enough for the purpose, and large doses have directly the opposite effect on resistance from what is desired.

These principles should, then, be borne in mind in planning the treatment for any individual type of case.

Arsphenamin dosage is determined by the weight of the patient and not by an empirical code. Since neo-arsphenamin differs from arsphenamin in having only two-thirds the arsenic content, it has been generally accepted that for equal effect one-third more neo-arsphenamin than arsphenamin must be given. This chemical estimation cannot be trusted, because the therapeutic effect of the arsphenamins is apparently dependent on a number of factors besides the absolute arsenic content. The nearest approach to an attempt to compare the two on a therapeutic basis has been that of Schamberg, Kolmer and Raiziss, who, by comparing the destruction of trypanosomes in the blood of the rat by the two preparations, suggested that the therapeutically equivalent dose of neo-arsphenamin as compared with arsphenamin is about double that for the latter drug. On this formula I have been proceeding for some time with at least no untoward effects.

An accepted full dose for arsphenamin is 1 dg. for each 25 pounds of body weight. For neo-arsphenamin, the therapeutic equivalent would be 2 dg. The initial dose should be one-half the full dose in most cases. Two-thirds of the full dose is the upper limit of the resistance-building dose for long courses, and half the full dose by weight is the lower limit of any widely accepted system at the present time. Very small doses have, to judge from experimental studies, a stimulating rather than a destructive effect on the organisms, and should not be used. They are at least demonstrably therapeutically ineffective.

The mode of administration of arsphenamin has so much influence on the matter of repetition of doses that it should be considered next. The original technic was intramuscular. It was abandoned in favor of the intravenous route, to do away with the pain and necrosis so often attendant on the earlier intramuscular injections. Ehrlich himself felt that, if it were easily available, the intramuscular route was the best from the standpoint of the effect on the disease, which seemed to be the better for the prolonged absorption possible in this way. Voegtlin and Smith have shown that the trypanocidal activity of arsphenamin is as great by the subcutaneous or intramuscular route as by the intravenous, and Craig showed that the effect on the Wassermann reaction was more pronounced. With all these arguments in favor of the intramuscular administration, the intravenous technic, because of its freedom from immediate discomfort, seems to have triumphed. None the less, several able therapists have adhered to the intramuscular route, and the gradual perfection of the technic seems to be bringing about a revival of the method which, with the perfection of some less irritating but effective preparation such as sulpharsphenamin, may ultimately find general acceptance. The comparative freedom of intramuscular technic from all but local complications, and its technical simplicity, would make it a godsend to the average physician.

When arsphenamin is given intramuscularly, the prolonged absorption and slow elimination make comparatively few doses necessary, four to six in the entire treatment according to Sutton's technic. Courses of six to eight injections of neo-arsphenamin are used in infants by Fordyce and Rosen. The intervals between injections are one month in Sutton's technic, owing to the slower absorption of arsphenamin, and one week in that of Fordyce and Rosen. In the intravenous administration of the drug, spirillicidal effects are secured by intervals of one to two or three days between doses. If a one-day interval is adopted, three or four doses in succession should be a maximum, and a rest interval will be necessary to allow excretion to catch up with intake. From six to twenty injections can be given at three-day intervals, if closely watched. It seems at times as if the closer intervals and larger doses were metabolized and eliminated with less disturbance than the large doses at longer intervals. The six-injection, seven-day-interval course is in common use and has on the whole a favorable tradition behind it, for both spirillicidal and resistance-building effects. It is therefore a good course for latent and late syphilis. Early in the disease, if the drug is properly tolerated, the intervals and doses should be shorter, especially at the beginning of the first course when a spirillicidal effect is urgently needed. The resistance-building effects reach their maximum on an interval of from seven to fourteen days, with courses of six to eight or ten injections of one-half to two-thirds the maximal dose.

Toxicity, stability and variability in therapeutic effect are three elements which should be borne in mind by those who work with the arsphenamins. It is not by any means the reactionless administration, easy though it is for physician and patient, which has the most curative effect on syphilis. In fact the work of Voegtlin and Johnson indicates that the more toxic preparations have the greater effect. There are, moreover, great variations in the therapeutic effectiveness of neo-arsphenamin in particular, and this drug is especially subject to deteriorating influences after packing. These two considerations alone should be enough to give pause to those who are inclined to seek the "lazy man's refuge" in the form of neo-arsphenamin for any and every purpose. The worthlessness of the drug may not be apparent from any external appearance or behavior, yet, as was recently shown in British practice, its spirillicidal power may be almost nil. It is common practice for manufacturers to use low toxicity as an argument for the use of their preparations. Fortunately, in this country, the Public Health Service control of therapeutic efficiency, as measured in trypanocidal power, is a partial protection. On the other hand, neo-arsphenamin in particular may undergo such pronounced deterioration after it is on the market that the physician who buys infrequently or from stale lots can scarcely know what he is getting.

The physician should not in general permit himself to think of the therapeutic effects of arsphenamin as those of arsenic per se. While the late complications have a disagreeable trick of being arsenical, the action of the drug is a thing *sui generis*. Schamberg believes that the amino group is as important as the arsenic in attaching the drug to the organism, so to speak. The combination into which the drug enters in the body is essential to its effect, and is, as in the case of mercury, not that of the metallic ion alone, but of a protein combination. Once disabused of the idea that all that is needed to duplicate the effect of arsphenamin is some organic form of arsenic, the physician will not so readily be deceived by absurd claims for such preparations as sodium cacodylate and so forth, which have done untold harm in the treatment of syphilis.

A comparative estimate of arsphenamin and neo-arsphenamin is one of the opinions much sought from every syphilographer. It may be fairly said that direct and complete evidence for the settlement of the question does not as yet exist. I insist on the use of arsphenamin whenever there is any outlook for a radical result, and in my service it is used in the proportion of seven doses to one of neo-arsphenamin. The arguments advanced in the preceding pages are important. Arsphenamin is more stable, more uniform therapeutically, less subject to deterioration, has a higher trypanocidal index than even the difference in arsenic content would explain. Neo-arsphenamin unquestionably has its uses, and there are undoubtedly highly effective lots available from time to time. It is excellent for children, in whom the technical difficulties are sometimes serious, and for the patient in poor condition. It is milder, less irritating to the kidneys, and non-hemolytic in solution. It does well if there is no therapeutic urgency. But if heavy and dependable treatment must be given day in and day out, it is quite generally conceded that arsphenamin is less tricky, perhaps more reactive, but more constant and trustworthy in its effects.

Silver arsphenamin, after two years' use in Europe, is being vouched for by several American observers as being therapeutically as effective as either arsphenamin or neo-arsphenamin. It has the strong endorsement of a number of German observers, but has been called in question in this country. It is given in doses of 0.1 to 0.25 gm. dissolved in 5 c.c. of cool distilled water for each decigram. It is then diluted with 0.4 per cent sodium chlorid solution to a dilution of 20 c.c. per decigram. Sulpharsphenamin, a compound closely related to neo-arsphenamin but suitable for intramuscular use, has been studied in this country by Voegtlin. It is intermediate between arsphenamin and neo-arsphenamin in many respects and, when given intramuscularly in 30 per cent solution, is said to have a lower immediate but a higher ultimate trypanocidal value than either. It is as yet under clinical investigation, but has a promising future.[3]

The Technic of Arsphenamin Administration; General Considerations.—Regardless of the method to be employed, all forms of arsphenamin administration have certain points in common. These concern first of all the preparation used. It has been repeatedly shown that the American-made arsphenamins, approved and controlled by the United States Public Health Service, are fully the equal, if not the superior, of European products, so there is no particular advantage in insisting on foreign-made arsphenamin. The ampule should be intact and the drug normal in color, odor, and consistency. *The label should be read.* The ampule may be tested by soaking it in a disinfectant solution which should reveal any slight perforation or crack. The label should be removed in the process. The color of arsphenamin is a light canary yellow, that of neo-arsphenamin a darker yellow. There is a corresponding difference in the color of the solutions. While discolored lots may be entirely safe, it is generally wiser for the average physician to reject a product which is abnormal in appearance. The odor of both preparations is faintly suggestive of garlic. If the odor is very pronounced, or has a pungency suggesting decomposing urine, the drug should be rejected. Arsphenamin is more difficult to dissolve than neo-arsphenamin and the instructions of the manufacturer with respect to the temperature of the water should be rigidly followed. Neo-arsphenamin which does not dissolve *readily and completely in cool water* may have an unusual toxicity, and should be rejected.

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[3] The use of buffered arsphenamin, prepared with glucose or gelatin, is under investigation and has a promising future because of reduced toxicity without loss of therapeutic effect.—Author.

The physician must, at the outset, grasp the fact that arsphenamin forms an acid solution when first dissolved that will produce almost immediate death if injected with a syringe after the technic of neo-arsphenamin. It must be neutralized with sodium hydroxid solution, precipitated and redissolved, and given, much diluted, by the gravity method. Neo-arsphenamin dissolves easily and promptly, is neutral, and may be given in concentrated solution. *Read the labels.* The physician who cannot mix his own arsphenamin and neo-arsphenamin should use the ready prepared solution of arsphenamin or give up the work entirely.

All arsphenamin administration calls for surgical asepsis. Glassware, tubing, syringes, needles, and so forth, are most conveniently sterilized by boiling. In larger clinics with special facilities, the needles may be baked at a temperature of 240° F. for one hour.

Whenever water is used in the preparation of arsphenamin, but particularly for the purpose of intravenous injection, certain methods of preparation have become essentially standard. These include the triple distilling of the water, avoiding exposure to air in order to prevent the reduction of the hydrogen-ion concentration by absorption of carbon dioxid. In this process of redistillation, the first and last fifths of the distillate from a given batch should be discarded. Water thus prepared must be boiled for complete sterilization before it is used for mixing. Water should not be transferred from flask to flask or poured about indiscriminately after it is once prepared, nor should it be kept longer than twenty-four hours. The temperature of the water at the time of mixing should conform to the requirements of the manufacturer of the drug. Room temperature is satisfactory in preparing neo-arsphenamin and silver arsphenamin.

Glassware should generally be boiled in distilled water to avoid the accumulation of residue and deposits of lime salts on the glass. The boiling should be for a minimum of ten minutes, and to prevent breakage and chipping it is well to wrap the individual pieces in gauze.

All rubber tubing and corks which are to be used in arsphenamin work, as shown by Stokes and Busman, should be prepared by preliminary soaking for twenty-four hours in a 5 per cent sodium hydroxid solution, care being taken that the solution reaches all parts of the bore of the tubing. This removes from the rubber a toxic substance which may give rise to epidemics of "tubing reaction" when a new tube is employed.

In the preparation of arsphenamin ("606") a solution of chemically pure sodium hydroxid is essential. This should be a normal solution prepared by titration against normal hydrochloric acid protected from the absorption of carbon dioxid, if possible, by the use of a closed buret system.

The process of neutralization will be described presently. All arsphenamin and neo-arsphenamin solutions are rather easily oxidizable, neo-arsphenamin particularly. While arsphenamin may be made up in quantities as high as 5 or 6 gm. at a time, if it is used at a single sitting, neo-arsphenamin should never be made up in this way. Each individual dose of neo-arsphenamin should be prepared at the time it is given, and should be given without delay. Shaking and standing have an important influence on arsphenamin and neo-arsphenamin solutions. It has been shown by Reid Hunt and by Roth that colloidal changes take place in the arsphenamin solution after mixing, which make it desirable to allow the batch to stand for from twenty to forty minutes after it is made. Neo-arsphenamin, on the other hand, must never be allowed to stand. Shaking the solution in the process of preparation has very little effect on arsphenamin solutions. On the other hand, it rapidly increases the toxicity of neo-arsphenamin. In the same way, squirting the solution of neo-arsphenamin back and forth by aspiration and ejection from a syringe, with a liberal spraying of air bubbles through the solution, also increases the toxicity.

All types of arsphenamin solutions, except those used intramuscularly, should be filtered through a glass adapter containing a small cotton pledget, or, in the case of dilute solutions, through a funnel with a sterile cotton pledget previously washed through with the hot, specially distilled water.

The question at once arises, how far the general practitioner may be expected to apply these special refinements which the experience of large clinics has shown to be essential to a uniform, smooth-running practice. It may fairly be said that any physician who plans to devote a considerable portion of his time to the treatment of syphilis should install the necessary apparatus and personally supervise the details of the technic enumerated. The isolated physician, obliged to treat occasional cases, should conform to these details as closely as possible. Fortunately the ingenuity of various manufacturers of arsphenamin has materially simplified the work of the isolated physician. Properly distilled water in ampules sufficient in amount for the preparation of neo-arsphenamin solution may be purchased directly with the ampules of the drug from certain manufacturers. Ready prepared arsphenamin in a solution of the proper concentration, in a sealed glass container, may also be obtained. This preparation is manufactured in accordance with the technic of Loewy, which consists essentially in driving off all the air from the arsphenamin solution after it is made so that it may be kept for a considerable period of time without risk of oxidation. Arsphenamin prepared in this manner exhibits, of course, the peculiarities of the brand of arsphenamin from which it is made. In my experience, the solutions are also somewhat more alkaline than the ordinary. The isolated physican would certainly be wiser to trust to a preparation of this sort than to allow an inexperienced nurse or pharmacist to prepare his solution for him from doubtful ingredients and under uncontrolled conditions. In general, it may be safely said that the physician who, in the light of modern knowledge of arsphenamin administration, dabbles in concentrated solutions and tap water mixing, is criminally negligent and foolhardy. Arsphenamin can be given on a woodpile with a fountain syringe and a hypodermic needle in cases of extreme emergency, but this does not justify the equivalent of such practice under ordinary conditions.

Technic of Intramuscular Injection.—The following is a quotation of the intramuscular technic employed by Sutton in the use of arsphenamin:

"All instruments and utensils and the 4 per cent sodium hydrate solution are sterilized by heat. . . . The arsphenamin (0.4 to 0.6 gm.) is dissolved in 6 c.c. of sterile water by the aid of rough surfaced glass beads. Four drops of a 1 per cent alcoholic solution of phenolphthalein are placed in the mixture to serve as an indicator, and the sodium hydrate solution is then added, drop by drop, with a small pipet, meantime vigorously shaking the mixture until the resulting emulsion is slightly but permanently pink in color. The mixture is then drawn into a 10 c.c. all-glass syringe and the injection immediately made into either the lumbar muscles, or better, into the gluteal muscles. Care must be taken to place the dose properly in the middle of the muscle mass. There is commonly some lumbagolike pain for a few days, but, if the dose is properly prepared and injected, this is seldom great enough to incapacitate the patient for ordinary labor. The main points to be considered in preparing the drug for injection are slight alkalinity (for this reason a 4 per cent NaOH solution is preferable to the 15 per cent generally recommended) minimum bulk, and absolute cleanliness."

The dose is equally divided between the two sides. The technic employed by Fordyce and Rosen in the treatment of syphilis in infants by means of neo-arsphenamin intramuscularly is substantially as follows: The dosage scale ranges from 0.1 gm. for infants from two to twelve weeks of age; 0.15 gm. from three to nine months of age; 0.2 gm. from one to two years of age; and 0.25 to 0.3 gm. for children three years of age. The neo-arsphenamin must be specially prepared for intramuscular injection and be neutral, or necrosis may result. A special needle, ½ to 1 inch long, and 19 to 20 gage, with a curved stop or guard to hold it firmly in place in the buttock, is necessary. The drug is dissolved in 3 c.c. of water, and half injected in each buttock, close to the gluteal fold. The needles as purchased should be specially sharpened.

Preparation of the Arsphenamins for Intravenous Injection.—Arsphenamin, "606," in aqueous solution, it is well to repeat, is strongly acid and must invariably be neutralized with sodium hydroxid before administration. The arsphenamin should be dissolved in the specially prepared water, shaking if necessary but as little as possible. It is best to powder the drug on to the surface of the water in a large Erlenmeyer flask, which avoids to some extent the formation of a bolus of air-containing granules. When the drug is completely dissolved, the product is a light yellow, clear solution. A number of recent investigations have contributed much to the technic of neutralization of this solution. Two salts are formed in the process of adding sodium hydroxid to the acid arsphenamin solution. When the addition of sodium hydroxid is begun, the first thing to appear is the insoluble arsphenamin base, precipitated out by the neutralization. As the addition of sodium hydroxid progresses, this base begins to go into solution as the monosodium salt of the arsphenamin base. When the addition of sodium hydroxid is continued still further beyond the point of actual precipitation, the disodium salt forms in increasing proportion. The best practice of the last several years has been the effort to obtain the disodium salt in maximal proportion. In order to do this, the immediate addition of a definite amount of normal sodium hydroxid solution (0.85 c.c. for each decigram or 8.5 c.c. for each gram of arsphenamin) is desirable. This can be measured directly into the solution from the closed buret. The result is a rapid precipitation and resolution yielding a definitely alkaline solution of the disodium salt. If the drop-by-drop method is employed, a fresh 15 per cent solution of sodium hydroxid should be used; the proportion of the monosodium salt will be much higher, because the adding of alkali is stopped when the last visible trace of precipitate disappears. On account of the fact that occasionally such solutions "work back" toward a slight acidity, it is generally advised to add several minims of the sodium hydroxid solution after neutralization is apparently complete.

It appears from the recent work of Oliver Douglas and Yamada that the disodium salt has definitely greater agglutinating power for red blood-cells than the monosodium salt, and this consideration may, in time, lead to a partial return to the monosodium-salt technic. At present, however, it is better to adhere to the disodium procedure.

The amount of water to be used in dissolving a given amount of arsphenamin has been a matter of considerable discussion. Attempts have been made to give arsphenamin in concentrated solution, but, while there is no question that it can be done, the method is tricky and unsafe. The Public Health Service standards advocate the administration of 30 c.c. of the specially prepared water for each decigram of arsphenamin, but in my experience, 20 c.c. for each decigram has proved entirely satisfactory. It is not necessary to employ the full amount during the mixing process, but dilution may be carried out just before administration. After the arsphenamin solution is neutralized, it should be allowed to stand from twenty to forty minutes before the administration is begun.

The odor, solution, and so forth of neo-arsphenamin have been described. The original neo-arsphenamin technic called for a dilution of from 10 to 20 c.c. for each decigram. Ravaut showed that the amount of solution could be reduced to 1 c.c. for each decigram without the production of reaction, and Alexandrescu-Dersca has shown that a full dose may be dissolved in as little as 2 c.c. These high concentrations are, however, undesirable because hard to control, so that it is my practice to use at least 2 c.c. for each decigram of neo-arsphenamin. This can easily be administered with the ordinary 20 c.c. Luer syringe.

Preparation of the Patient.—The preparation of the patient for arsphenamin administration should consist of a physical examination and examination of the urine. The physical examination should be adequate from the syphilologic standpoint, and take into account all evidence of involvement of important structures by the disease, and the acuteness of the process. Dietary preparation should consist of fasting (patient should miss one meal), and, if constipation is the rule, a laxative (no purging) before injection. It is also of advantage to have the patient rest for several hours before treatment, if this is possible. At the time of receiving the injection, the patient should lie on a suitable table, with the head slightly elevated. The arm, neck and upper thorax should be exposed, and the site of injection (usually the median cubital vein) sterilized with tincture of iodin. Patients whose skins are reactive to iodin or who have had a dermatitis in the past should be sterilized by vigorous scrubbing with alcohol. The use of a local anesthetic, 2 minims of a 2 per cent cocain solution, has been an invaluable aid to good technic in my experience. This should be injected after the application of the tourniquet, care being taken to raise a small wheal in the skin immediately over the surface of the vein, and not to inject the anesthetic intravenously. The smallest size of hypodermic needle (24 or 27 gage) should be used. When neo-arsphenamin is to be administered with a small needle (22 gage), it is usually unnecessary to employ a local anesthetic unless the vein is reached with difficulty.

Technic of Intravenous Injection.—A high degree of proficiency in intravenous technic is obtained only with difficulty and by dint of much practice. An average degree of proficiency may be developed within a comparatively short time by learning a rigid system of approach, consisting of a series of motions which, if exactly repeated, bring about the desired results in most cases. The items of this technical procedure include: (1) preparation of the needle point; (2) the position of the arm; (3) the tourniquet; (4) the identification and preparation of the vein; (5) the technic with the Schreiber needle; (6) the syringe technic; (7) the prevention of accidents and complications.

Preparation of the Needle Point.—For the intravenous administration of arsphenamin by the gravity method, the Schreiber needle (Fig. 2) is satisfactory. The needle should be of steel or tempered gold, 18 or 20 gage. It is important that the guard should have enough of a curve to receive easily the ball of the index finger. For the syringe technic, the needle should be straight, 1½ inch 22 gage steel, tempered gold, or platinum. The bevel point of a needle, as ordinarily purchased on the open market, is too long, and the point itself has a lancelike prolongation which makes its actual position in entering or after entering the vein a matter of great uncertainty. The ideal needle point should, moreover, not present the semicircular cutting edge which it usually develops after several attempts to shorten or sharpen the bevel. By holding the needle slantwise on the stone, the bevel may be brought down to a point of medium length. If the bevel is shortened too much, the needle will stick and pile up the tissues over the surface of the vein, with resultant stripping. On the other hand, if the point is rounded, even though sharp, it cuts a slit in the vein which makes subcutaneous bleeding likely and may injure the vein sufficiently to cause thrombosis. Long beveled needles, especially in veins of small caliber, are apt to pass through the far side of the vein before the entire needle is within the lumen. Long beveled needles have, moreover, a trick of yielding a return of blood through that part of the opening which lies within the vein, while infiltration of the tissues results from leakage through the part of the opening which still lies outside the vein.

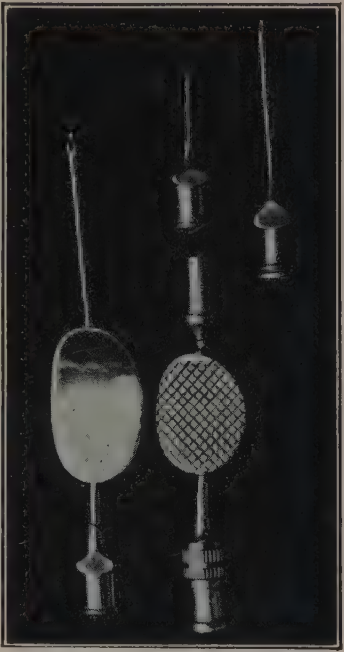


Fig. 2.—The Schreiber Needle (left), and an Adapter to which Smaller Hypodermic Needles can be Fitted for Fine Veins. The needle here shown has the proper length of bevel and form of point.

Position of the Arm.—The arm should be extended at right angles to the body, resting on a slightly slanting support at desk level, directly before the operator. The entire arm and neck should be bare and unconstricted.

The Tourniquet.—The Esmarch elastic bandage makes the most satisfactory tourniquet we have ever employed. Rubber tubing fastened with a hemostat or an inelastic compressor, such as a towel or bandage, is certainly not a satisfactory substitute. The tourniquet should be applied from behind, forward, the strands crossing each other and pressed downward on the arm without being gathered into a knot. The resultant pressure is much like that secured by a blood-pressure cuff without the loss of time incident to inflation. If the patient must hold his own tourniquet, this can easily be done by a single twist of the strands. When an assistant is available, a better distention can be secured and there is less likelihood that the veins to be injected will escape compression by passing under the knot. The assistant should be taught to release the tourniquet carefully and without jarring. There should, moreover, be no pulling aside or twisting of the skin which might flatten the vein.

Identification and Preparation of the Vein.—The vein to be used should be selected, if possible, before the tourniquet is applied. Palpation is sometimes of more assistance than inspection for this purpose; one finger should be trained to tactile acuteness. Cross stroking or light downward pressure will often identify the yielding ridge of an invisible vein. Previous thrombosis may be identified by the jerk of the obliterated cordlike vein under the finger.

Clenching of the fist after the tourniquet is applied usually produces a satisfactory dilatation. If it does not, several sharp slaps at the site of injection will often cause a temporary dilatation due to vasomotor paralysis. Poorly developed veins may be made distinctly more accessible and more distended by soaking the arm in hot water and by the systematic use of daily arm gymnastics, including exercise of the forearm and brachial muscles, for five to ten minutes twice a day. The inspection preliminary to entering the vein should include an estimate of its direction and depth, because entry should always be made in the line of direction of the vein, to permit the needle to advance well beyond the point of puncture. Thin arms are sometimes more difficult to enter than fleshy ones, because of the imperfect fixation of the vein by connective tissue. Scarcely visible veins in fleshy arms are sometimes very much nearer the surface than their appearance and "feel" suggest. The toughness of the skin over a vein at the wrist may make what seems an easy prospective entry quite difficult, and care must be taken to avoid jerking. The point for entry should be as near the operator and as far from the heart as possible, so that, if a second puncture becomes necessary, it may be made above the first to avoid leakage of the injected liquid through the original puncture wound.

One movement is absolutely necessary to the technic of entering the vein. It consists in the drawing downward of the tissues of the forearm by the flats of the fingers of the left hand, in order to fix the vein by tension on the surrounding tissue. This movement should become absolutely automatic.

Technic with the Schreiber Needle (Gravity Method).—The Schreiber needle should be held between the thumb and first two fingers of the right hand in prolongation of the index finger, much as a pen is held in writing. The fourth and fifth fingers rest on the flat surface of the forearm and are held firmly in position, thus fixing the needle and preventing jerking movements. All movements of the needle should be accomplished by extending or flexing the fingers, and not by movements of the wrist and elbow, which are apt to be coarse and ill-judged. Two distinct movements should be made, the first passing the needle through the skin over the top of the vein, puncturing the wheal produced by the cocain. If an interval of ten seconds is allowed after the injection of the local anesthetic, the puncture will be practically painless. When the point is clearly visible in the skin above the vein, the hub of the needle may be elevated and the needle advanced downward, then up and forward along the course of the vein. The motion is somewhat akin to sewing, and unless the upward dip is made, there is risk of transfixing the opposite wall. A clear entry is signalized by a free flow of blood from the opening of the hub and, when this occurs, the needle should be advanced 1 cm. further up the vein, care being taken to elevate the point slightly and to bear downward with the fingers so as to avoid transfixing. At no time during this procedure should the fingers of the left hand be released from tension on the skin of the forearm. If the flow of blood is free, the adapter attached to the end of the rubber tube from the container should at once be inserted into the needle hub, a small amount of the arsphenamin solution being first allowed to escape in order to expel all air. The right hand continues to hold the needle fixed in position from start to finish. A proficient operator may, under proper circumstances, support the needle with a cotton pledget and fasten it in place with adhesive plaster, but this procedure is not permitted on my service. When the injection is completed, the flow of liquid is stopped by pinching the tube with the left hand immediately behind the adapter and withdrawing both needle and tube at the same time, while the nurse covers the needle point with a cotton pledget under pressure. If this movement is properly executed, no leakage into the tissue will result.

Syringe Technic (*Neo-arsphenamin*).—The syringe technic is usually employed in the administration of neo-arsphenamin. It is very important that the piston should work smoothly and freely but without leakage in the barrel. The solution to be injected is aspirated into the syringe through a filter-tip, or even through the needle alone, if the needle is small. The tourniquet having been applied and the survey of the vein completed, the left hand pulls down the skin of the forearm, fixing the vein as in the Schreiber technic. The syringe is held flat on the palmar surface of the four fingers of the right hand and kept firmly in place with the thumb. The backs of the four fingers are then laid firmly on the patient's forearm, steadying and fixing the wrist, which prevents haphazard movements. The needle is directed along the course of the vein and an entry made in two motions, precisely as in the Schreiber technic. This method is, in my experience, greatly superior to all methods involving movements of the arm and wrist, which are apt to be coarser and less controllable.

Inasmuch as the needle used in this technic is smaller, it is unsafe to rely on a return of blood against the weight of the syringe piston. The third step, therefore, consists in holding the syringe firmly in place by the right hand, while the left hand releases the skin of the forearm and draws back strongly on the syringe piston. If the needle is free in the vein, a spurt of blood shoots across the clear liquid in the syringe barrel. Unless this spurt of blood occurs, it is unsafe to proceed without further consideration. As soon as the spurt of blood is obtained, the left thumb forces in the syringe piston against the pressure of two fingers embracing the end of the barrel or guard. During this time the right hand, holding the syringe, has remained absolutely fixed by firm pressure on the patient's forearm, keeping the needle exactly in place.

Prevention of Accidents and Complications.—Arsphenamin and neoarsphenamin have a profound local irritant effect when even a small amount is injected into the subcutaneous tissues. If the amount of the injection is considerable, a dense brawny infiltration develops, the center of which may undergo necrosis, leaving a slough which is exceedingly slow to heal. The amount of pain and disfigurement which may be produced by a single such blunder in technic may be very serious and form the occasion for medicolegal action. Almost unbelievable technical errors may occur, such as the infiltration of the median nerve in the cubital space instead of the vein. Such blunders are, of course, quite inexcusable and do not occur if the physician has had proper technical training.

All the details of the technic described are intended to prevent the leakage of any of the drug into the tissues, as well as to secure its delivery into the blood-stream. Wipe the needle clean of all arsphenamin solution before introducing; demonstrate the patency of the needle by aspirating a small amount of the freshly distilled water through it with the syringe before beginning the puncture, and wash out the needle after each injection, in the same way, and sterilize by boiling. If, after the introduction of the needle, a free flow of blood cannot be obtained, the following procedures may be tried successively, to ascertain the difficulty: (1) depress the needle point without advancing; the bevel may be shut off against the top of the vein; (2) feel for the needle point with the free hand; if it is still above the vein it can be easily felt; (3) the syringe piston may stick and may be loosened by twisting in the barrel and pulling backward; (4) transfixing of the needle point in the opposite side of the vein, provided the vein has not been punctured, can be remedied by slowly lifting up on the needle point while the needle is withdrawn a short distance; it will come away with a quick snap if it is simply caught in the opposite wall; (5) the needle may be then quickly advanced with the point raised as high as possible, flattening the needle down to the surface of the arm as much as possible; (6) if the above measures fail, the needle may be withdrawn until the point is just short of the skin puncture, and another advance made under guidance of the palpating finger; (7) if this procedure fails twice, the needle should be withdrawn and tested for patency and the point carefully examined; while this is being done, elevation of the arm with pressure over the vein by a cotton pledget may make it possible to use the same vein again; (8) if leakage of blood into the surrounding tissues occurs, begin over at another point; never attempt to inject through a hematoma; (9) to inject a little and ask the patient if it hurts is evidence of inefficiency; never proceed to inject until you feel sure that the needle is in the vein, even though subsequent events may prove it is not; (10) one skin puncture may be used for several attempts, and every effort should be made to have this one suffice; (11) cutting down on the vein is absolutely inexcusable in these days, and patients whose veins seem so inaccessible as to suggest the need for such a measure should be sent to an expert; (12) patients with florid syphilis should always be treated last; (13) the use of the jugular vein and of the anterior parietal or other prominent skull veins in heredosyphilitic infants is technically not very difficult, but requires efficient assistance and some experience; we have never had occasion to use the superior longitudinal sinus and do not recommend this technic; and (14) fine steel hypodermic needles should be used in all intravenous work on infants and small children.

Rate of Injection.—It has been shown that the rate at which a solution of either arsphenamin or neo-arsphenamin is introduced into the circulation has a pronounced influence on reaction, and especially on the production of the nitritoid crisis. The rate of injection of arsphenamin recommended by the United States Public Health Service is 0.5 dg. (equivalent to 10 c.c. arsphenamin solution) each minute. It is possible to increase this rate to 1 dg. each minute with only a slight increase in the incidence of reaction. The time of injection should be carefully controlled with the watch and not be left to guesswork, because such estimates invariably result in rapid injection. The rate of flow of the solution by the gravity method can be regulated by a screw clamp. The injection of neo-arsphenamin should not be at a more rapid rate than 2 dg. each minute. Since the amount of solution is small, the constant temptation is to exceed this limit.

After-care of the Patient.—The conditions of ordinary practice make it difficult to give patients ideal after-care following arsphenamin treatment. Whenever it is possible to do so, the patient should be kept in bed for from eight to twenty-four hours following injection. It is only by this means that one can thoroughly control his technic so far as the incidence of reactions is concerned. If it is impossible to do this, the patient should remain lying in the office for at least an hour, after which he may go to his room under suitable escort. When ambulatory measures of this sort must be routinely employed, it is safe to use only moderate dosage rather than to attempt strenuous procedures. The patient should invariably be instructed to eat only very lightly of soft foods and, if he can do so without inconvenience, to fast for the ensuing twelve to eighteen hours. The morning of the day after the injection, the patient should take a brisk cathartic, consisting of an ounce of castor oil or of epsom salts, which should be followed by several free evacuations. Inasmuch as most of the arsphenamin is eliminated through the bowel, this measure is extremely important in preventing reaction from reabsorption of the decomposition products of the drug. If signs of reaction appear, it is much safer to see the patient personally at once than to attempt management of his case by proxy or over the telephone. If possible, the physician should make at least one call within the ensuing twenty-four hours.

If patients are hospitalized, the temperature and pulse rate may be noted at four-hour intervals. In case the bowels do not move following the administration of a cathartic, an enema must be used, or the cathartic repeated. The patients should be strongly impressed with the importance of this matter.

Complications of Arsphenamin Treatment.—Not everything that happens after arsphenamin administration is due to arsphenamin or to arsenic. None the less the physician should critically watch his patients for signs of reaction, and endeavor constantly to reduce the incidence of complications. To hand out arsphenamin "shots" like drinks over a bar, with no control or responsibility for what happens beyond the door, is malpractice.

Pain.—Burning pain at the site of injection warns the physician that he is infiltrating the tissue. Insensitive or obtuse patients may not complain until the infiltration is serious, or may even regard the pain as expected, so that it should always be inquired for. Pain felt up the arm after injection is begun usually means that the rate of injection is too fast, or that the solution is too alkaline. It may be followed by phlebitis. The treatment of pain at the site of injection is to stop and begin over. By slow or intermittent administration, it may be possible to complete an injection complicated by pain up the arm.

Collapse.—This is the sequel of injecting acid arsphenamin or a highly toxic solution. The patient becomes pale and pulseless and usually dies within a few minutes. If there is any time to act, inject Fisher's solution intravenously, 200 c.c., and begin its rectal administration at once. Epinephrin may be given, but will probably do no good.

Nitritoid Crisis.—This reaction usually begins after the injection has been partly given, and is often a sign of too rapid injection. A choking sensation, cough, gasping, edema, and intense flushing of the face, with loss of consciousness if the injection is continued, are the symptoms. The patient should be watched all the time while receiving treatment and, if this reaction appears, the injection must be stopped. Epinephrin solution, 1:1,000, 10 to 20 minims according to severity, should be given subcutaneously. The epinephrin solution should be always at hand. Patients who react repeatedly in this way may be given atropin hypodermically, $\frac{1}{50}$ gr. twenty minutes before injection, and the dose of arsphenamin may be split in two parts, the first one-tenth being given forty minutes before the remaining nine-tenths.

Vomiting.—If vomiting occurs while the patient is on the table, it usually indicates a full stomach. After injection it is part of a gastro-intestinal reaction and comes on from four to eight hours after injection. It may be relieved to some extent by copious drinking of warm water with emesis, followed by cracked ice, carbonated waters and ginger ale. Sodium bicarbonate may give relief.

Hysteria.—Minor or major attacks of hysteria may complicate arsphenamin treatment in nervous patients. Pseudosyncope, spasms and contractures are the usual manifestations. The diagnosis of hysteria should not be made except by elimination.

Necrosis and Infiltration of the Site of Injection.—This is always an evidence of a serious lapse in technic. The slough which may follow may be months or even years in healing. If even the slightest infiltration has occurred at the time of injection, as much solution as possible should be massaged out through the puncture wound, wet saline dressings and ice-bags applied, and the extended arm placed at rest. Most cases will involute under such treatment. "Bluffing it through" by doing nothing should not be attempted. If there is much stiffness or contracture, massage, heat and passive movement may be begun in ten days or two weeks.

Phlebitis.—Examination for phlebitis should always be made before beginning an injection, since the onset may be without symptoms. The vein becomes an incompressible cord. A solution which is too alkaline when injected too rapidly (with too large a needle) especially predisposes to this condition.

Late Gastro-intestinal Reaction.—The usual onset of such reactions is after eight hours. A light diet or fasting may prevent them, and rapid injection or poor mixing may be a predisposing factor. Certain patients have an idiosyncrasy which is expressed in this way. The technic for the prevention of nitritoid crises is of some help in gastro-intestinal reactions. An ice-bag to the stomach, gastric lavage, the measures for treating vomiting, and the administration of bismuth and paregoric in cases associated with diarrhea are all helpful. The physician and the patient should not take these reactions too seriously or reduce dosage unduly.

Tubing Reaction.—This reaction, the result of a toxic substance present in some brands of fresh rubber tubing, runs a typical course, beginning with a violent chill thirty minutes after injection, followed by a high fever, vomiting, diarrhea and prostration, with herpes and a gradual decline in temperature to normal after forty-eight hours. Such reactions occur in crops in clinics in which large numbers of patients are treated, and disappear after all the toxic substance in the tube has been dissolved by continued use. To prevent the reactions, all rubber articles used in intravenous work should, when new, be soaked or boiled in a 5 per cent solution of sodium hydroxid, being sure that the solution reaches all parts of the bore of the tubing.

Herxheimer Reaction.—This is not a reaction to arsphenamin, but a constitutional and local flare-up of the disease resulting from the therapeutic shock administered by the drug. While it may have no serious effects, or even a good effect in robust individuals with generalized infection but without grave local lesions, the flare-up may be serious or even fatal if it occurs in the heart muscle, the vascular system, the liver, or even in such a structure as the larynx, whose situation makes it important for the maintenance of life. In early cases the Herxheimer reaction is easily visible in the form of a flare-up of the eruption, if present. Most localized, visible lesions show it. A rise of temperature accompanies the reaction in acute syphilis, but subsides within a few hours to two days. It follows the first, sometimes also the second injection. In late cases no constitutional symptoms except those resulting from damage to a special structure arise, and the flare-up may develop more slowly. The reaction must be expected at any and all stages of the disease, and be planned for, if a flare-up in a local lesion is likely to do harm. The proper preparation is mercurial, the slower and less intensive action preventing the acute symptoms. A soluble mercurial salt intramuscularly, two weeks of rubs and medication by mouth will usually take the edge off a Herxheimer reaction, but in some cases preparation must be longer, especially in case the heart or liver is affected.

Hemorrhagic Encephalitis.—This is the most fatal and, fortunately, one of the rarest reactions to arsphenamin. It is the result of vascular injury to the brain, with the development of edema and multiple hemorrhages. The usual onset is subsequent to the fourth injection, and symptoms may not appear for several days. Depression sets in, which passes slowly into a stupor with muttering delirium, or even with excitement suggesting delirium tremens. Alcohol seems to be a predisposing factor, so that confusion with it is possible. Finally after some hours the patient cannot be aroused, the breathing becomes stertorous, the face puffy. Death usually occurs within three days after the onset of symptoms. The vital element in prophylaxis and treatment is epinephrin, which, if used early and in large doses, may save the patient. Hypertonic sodium chlorid solution intravenously may be tried to relieve the cerebral edema. There is no known prophylaxis in the treatment régime except to beware of alcoholics and keep patients under observation.

Anuresis.—This condition is almost ipso facto evidence that un-neutralized arsphenamin has been given. If immediate death does not result, Fisher's solution in 200 c.c. doses intravenously and by rectum may result in recovery. Decapsulation of the kidney might be considered if this fails.

Jaundice, Hepatitis and Acute Yellow Atrophy.—Jaundice occurring after the administration of arsphenamin is not to be too readily interpreted as a reaction to the drug. It may be the result of a flare-up in a syphilitic hepatitis. In that case it will clear up on continuance of the treatment. It may be the result of gall-stones. It may be the result of a coincident catarrhal cholangitis. It may be the first warning of the fulminating onset of acute yellow atrophy of the liver, a rare complication of syphilis, and also of the administration of arsphenamin. Careful examinations should be made to determine the possible cause. Acute yellow atrophy is accompanied by profound prostration, with the appearance of crystals of tyrosin and leucin in the urine, a rapid enlargement followed by shrinkage of the liver, and death within a few days at the latest. Sodium thiosulphate may be administered on the supposition that arsenic may be doing the damage. Glucose may be given by rectum. In the less fulminating cases, recovery may occur.

It is important to distinguish the group of infectious cases of jaundice, which have been rather numerous in the past two years, since the epidemics of influenza, from the other types. Treatment for syphilis in these cases may predispose to jaundice, but the pathologic process itself seems to be an ascending infection from the duodenum. In one case which came to necropsy on my service, pus was found in the ampulla of Vater and in the common duct. There was evidence of duodenitis. The onset is likely to be preceded by an arthritic prodrome. In such cases, much relief is afforded by duodenal lavage and magnesium sulphate. A course of calomel and salts, followed by a soft diet, sodium phosphate, and ox gall in 10-gr. doses, shortens the course materially, although the duration is seldom less than from four to six weeks. When necessary, treatment may be continued with both arsphenamin and mercury through the course of the jaundice, although the dose should be reduced and neo-arsphenamin used.

Cutaneous Reactions.—These may range from the mildest to the most severe of complications. Urticaria may appear within a few hours after injection and respond to epinephrin and a cathartic. Morbilliform toxic erythema begins with a chill and a rise in temperature about twelve hours after injection, sometimes with high fever. The eruption appears the second day and the temperature subsides. Involution is usually spontaneous, although the physician may credit it to some procedure which he has adopted.

Itching of the skin after an arsphenamin injection, and the appearance of an erythematopapular eruption in the flexures and around the face, is a warning of one of the most intractable and serious of the complications of arsphenamin administration, exfoliative dermatitis. The physician must be constantly on his guard against it and instruct the patient to watch for its prodromes. While arsenic as such is a factor in its production, this is by no means the whole story, and focal and intercurrent infections, idiosyncrasy, hepatic insufficiency and external irritation may all be elements in its production. A similar eruption may result from the use of mercury by inunction or intramuscularly. Treatment consists first in discontinuing the use of arsphenamin on the first warning of dermatitis. Patients who show an inclination toward this type of reaction should not be handled by the general practitioner if there seems to be any occasion for continuing arsphenamin or, in fact, any kind of antisyphilitic treatment. If an attack threatens or develops, the patient may be given sodium thiosulphate (chemically pure) intravenously, in doses of 0.75 to 1.0 gm. every other day, for from four to six doses. Great care should be taken to prevent catching cold, and if focal infections are present they should not be tampered with during the attack. The oatmeal and soda bath used for from twenty to thirty minutes two or three times a day gives much relief in most cases. The bath is prepared by making up an oatmeal gruel to which is added a cupful of baking soda on cooling. The whole is strained through cheesecloth into a bathtub full of water at a temperature of 90° to 95° F. It is absolutely necessary to apply an ointment, preferably Lassar's paste without salicylic acid, immediately after the patient leaves the bath to prevent excessive drying. The stomatitis and conjunctivitis must be dealt with symptomatically. Alkalinization by mouth and Fisher's solution by rectum are of value. Diarrhea with colonic ulceration occurs in some epidemics. Patients with such conditions are much better cared for in a hospital in experienced hands than at home. If they survive the fourth week, recovery is probable. Arsphenamin treatment at any time in the future is attended with risk of recurrence.

Pneumonia.—Patients who have slight respiratory infections, especially during epidemics of influenza and so forth, may develop pneumonia after an arsphenamin injection. Such an occurrence likewise raises the question of insufficiently alkalinized arsphenamin.

Aplastic Anemia.—Moore and Keidel have called attention to this rare but grave complication of the administration of neo-arsphenamin.

Contra-indications to the Use of Arsphenamin.—Many apparent contra-indications to the use of arsphenamin may have arisen from faulty technic. There can be little doubt that the physician whose technic is faulty is kept so well reminded of the harmful possibilities that he is likely to reduce his use of the drug to the lowest possible amount. As a matter of fact, considering its arsenic content and its administration directly into the blood-stream, there are few drugs so remarkably foolproof as the arsphenamins. There do exist, however, certain contra-indications which may be enumerated as follows:

Arsphenamins are hepatotoxic and vasculotoxic, and for this reason should be used more cautiously in patients who have damaged livers, myocardial lesions, aneurysms and arteriosclerosis. Hypertension of the essential type, however, is not an intrinsic contra-indication. The existence of an acute process or extensive syphilitic involvement of a vital structure, because of the risks associated with the Herxheimer reaction, must be regarded as a relative contra-indication to the use of the arsphenamins until after mercurial preparation.

Arsphenamin should never be used until a physical examination of the patient has been made to determine the activity of the syphilitic process and the extent of and localization of damage. To treat a patient with arsphenamin simply because he has a positive Wassermann reaction, without studying his case from the standpoint of the entire disease, is a crime.

Arsphenamin is relatively contra-indicated, especially early and in large doses, in all cases in which rapid healing of the lesions will deprive the affected structure of its power of physiologic adjustment, with consequent inadequacy or breach of compensation. The myocardium, the vascular system, the liver, and so forth, are all examples of structures that may be seriously injured by rapid healing.

Respiratory infections are a relative contra-indication to the use of arsphenamin, especially on account of the intravascular agglutination changes that may provoke pulmonary congestion if the patient reacts (nitritoid crisis).

Patients with febrile processes tolerate arsphenamin poorly, unless the fever is due to syphilis, in which case the response is prompt. Pyelitis and tuberculosis as complications of syphilis may hamper the use of the drug, and rest in bed may be necessary before it can be employed. In all such cases, neo-arsphenamin seems preferable. Afebrile tuberculosis and renal conditions other than pyelonephritis, on the other hand, do not seem to contra-indicate a reasonable dose.

Previous extensive and severe dermatitis of any type is a relative contra-indication, and recent exfoliative dermatitis is an absolute contra-indication to the use of arsphenamin.

Primary optic atrophy of whatever cause has, in my experience, been a relative contra-indication to the use of the arsphenamins. Certain patients may tolerate the drug well, but a fair proportion are promptly made worse.

THE IODIDS

General Considerations.—Iodin was first administered by Martin of Lubeck, in 1821, in the form of burnt sponge for the treatment of venereal ulcers of the throat. In 1834 Wallace of Dublin employed potassium iodid, and pointed out the indications and contra-indications for its use. Under the influence of the French school the drug attained a recognized place in the treatment of syphilis, and, if anything, was rated higher than its real merits deserved. It has, however, a real place in the management of the disease which, while still ill-defined, is gradually approaching rationalization.

The action of iodids is entirely non-specific, in the sense that the drug as given has no spirillicidal power and does not apparently stimulate the body to destroy spirochetes. On the other hand, it does accomplish the resolution or healing of granulomatous tissue and, since the essential pathologic lesion of active syphilis is a granuloma, it exerts an indirect influence on the progress of the disease. The mechanism of its action, while not completely understood, is perhaps best explained by the theory of Jobling and Peterson, which maintains that the iodin ion combines with the unsaturated lipoids of the blood, which constitute the trypsin inhibitive mechanism. By thus inactivating the antitrypsin, the proteolytic ferments of the blood are released to bring about a lysis of the granulomatous tissue. The selective action on granulomatous tissue is explained by the observed excess concentration of iodin in such tissue, both in syphilis and tuberculosis.

Iodin is, therefore, an adjunct in the treatment of syphilis whose purpose is to dispose of the granulomatous and fibrous hyperplasias which characterize the disease in all structures. While it does not act on the organisms, theoretically at least, it exposes them by the lysis of the tissue in which they are present to the better action of spirillicides and resistance-builders, such as arsphenamin. It is, therefore, commonly spoken of as a "mobilizer" of spirochetes, a term that is especially popular in the recent revival of iodin treatment to meet the resistant and Wassermann-fast types of infection. The drug should never be used alone in syphilis, that is, without either mercury or the arsphenamins. It is especially valuable in conjunction with mercury, because arsphenamin has a certain amount of non-specific action on granulomas which mercury seems to lack. While it may be employed in early syphilis, it is preëminently adapted to use in latent and late syphilis, and in special types of lesions associated with plastic exudates such as the meningitides. It is theoretically useful in the resolution of vascular fibrosis, and is in fact one of the main reliances in cases of vascular syphilis of all types.

Various combinations of iodin have been proposed at one time and another, but as yet none has demonstrated a distinctive superiority over the simple sodium and potassium salts. Organic combinations such as "mirion," for example, while the subject of much controversial literature, do not as yet seem to have justified their existence.

Sodium and potassium iodid, while of the same molecular constitution, differ in their physiologic effects, according to the work of Osborne. Of the two, the potassium salt produces a larger proportion of sodium-iodin protein combination with the blood-serum. There is certainly a well-defined clinical impression that the potassium salt, while somewhat more irritating, is also more effective therapeutically.

Potassium iodid can be administered by mouth and by rectum, and sodium iodid by the same routes and intravenously besides. Potassium iodid can only be given in minute doses intravenously. The concentration of the drug rises rapidly after administration, and when given by mouth may be maintained at a fairly high level. Elimination is entirely by way of the kidney. Intravenous use gives high peaks of concentration with corresponding drops. The concentration of iodin in the spinal fluid can be greatly increased by intravenous administration, much less so by ordinary doses by mouth. The utility of intravenous use is, however, not yet conclusively demonstrated from the experimental side. Intraspinal use, recently tried, has no demonstrable value and may be dangerous.

Iodids share with bromids the power to induce in the body that state of allergic susceptibility of a non-specific type which is expressed by the luetin reaction in syphilitic patients. In other words, the administration of iodid to a normal person may cause him to give a positive luetin test and to react, as in the case of luetin, to colloids such as agar and so forth. This tissue allergy may be part of the non-specific defense mechanism of syphilis and may explain some of the favorable action of the drug on the disease.

Iodid by Mouth.—I believe that the potassium salt is preferable, if well tolerated. The drug may be used early in the course of the disease, especially if there are evidences of involvement of the nervous system. Two types of doses are recognized, the small dose, 5 to 10 gr. three times a day, and the large dose, 30 to 150 gr. three times a day. Idiosyncrasy seems more marked with small doses and certainly, so far as chemical analysis goes, the concentration of iodin obtained is much less. The therapeutic effect on granulomas other than syphilis is also better with larger doses. It is therefore my practice to use doses ranging from 20 to 150 gr. three times a day by mouth.

The ascending dose is a tradition of uncertain utility, because it often appears that by beginning promptly with a large dose the patient escapes reaction entirely. It is customary to increase the dose from 1 to 5 gr. each day until the maximum is reached. The dose should then remain at the maximum until the drug is discontinued or until reduction is forced by developing iodism.

The best time to give iodids is before meals on an empty stomach. The drug then quickly leaves the stomach with a minimal amount of disturbance. An aqueous 1:1 solution (not saturated) enables the patient to take 1 minim for each grain. Dilution helps to diminish intolerance, and the entire day's dose may be put in a gallon of water and drunk at odd times with good effect.

Sodium Iodid Intravenously.—This method, developed in the past ten years, evades some of the reaction-producing qualities of administration by mouth, and permits of a high concentration, especially in the spinal fluid. This concentration is to some extent proportional to the extent of meningeal reaction, as shown by Osborne, and hence the method is especially applicable to patients with high cell counts in the fluid, as in early syphilitic meningitis. The drug must be chemically pure and given in 10 per cent solution in specially prepared distilled water, as in the case of arsphenamin. The dose is from 2.5 to 10 gm. daily. Small veins may be thrombosed by it in time, so that it should not be used on "one-vein" patients. There is no object in giving less than 5 gm. daily, because equal concentrations can be secured by large doses by mouth. All patients, before receiving sodium iodid intravenously, should be given a two-day tolerance test by mouth. If iodism (not acne) develops, the intravenous method should not be used.

Complications of Iodid Administration.—The recognized reactions to the iodids include coryza, laryngeal edema, gastro-intestinal disturbances, and various cutaneous manifestations including iodid acne, vegetative and frambesiaform lesions, angioneurotic edema, acute bullous iodism, and exfoliative dermatitis.

Coryza.—The coryza of iodism usually appears with the smaller doses and within two or three days after administration is begun. It may clear up spontaneously as the dose is increased, or following a quick jump to a dose above 30 gr. three times a day. Discontinuing the drug and beginning over is less often helpful. An effort should always be made to push the dosage beyond the point at which the patient has this reaction. Sodium iodid by mouth or even at times intravenously may be tolerated when potassium iodid is not, but true iodism in general contra-indicates intravenous use.

Laryngeal Edema.—Laryngeal edema occurs only in extreme grades of iodid idiosyncrasy, or occasionally following the intravenous use of the drug. The appearance of pronounced hoarseness is a warning sign and it is better to discontinue administration than to push it too far. Laryngeal and bronchial spasm with severe asthma and coughing and wheezing may occur occasionally following intravenous administration. It is promptly relieved by epinephrin.

Gastro-intestinal Disturbances.—Gastro-intestinal disturbances with the administration of the smaller doses are rather common and may be avoided to some extent by large dilution and giving the drug before meals. The unpleasant metallic taste in the mouth due to the elimination of iodid in the saliva is in part responsible for the anorexia. Sodium iodid by mouth is somewhat less likely to produce reaction than potassium iodid and in the very few patients who, because of gastro-intestinal intolerance, cannot take iodids by mouth, intravenous administration may be substituted if necessary.

Cutaneous Reactions.—Cutaneous reactions to iodid have a wide range and vary from an insignificant acne to acute fatal bullous iodism. The mild iodid acne can be controlled to some extent by reduction of the carbohydrates in the diet, and the use of lotio alba or Vleminckx's solution (liquor calcis sulphata N.F.) diluted one part to sixteen of water. The fungus and vegetative types of lesions are much more rare than acne, and are an expression of an idiosyncrasy which probably cannot be overcome. Acute bullous iodism is the product of an extreme idiosyncrasy and may be fatal. Intravenous administration of iodid without preliminary testing of the patient's tolerance may precipitate an extreme grade of general erythema and edema. In patients who are susceptible to exfoliative dermatitis, the drug has been known to produce an outburst of this complication. Angioneurotic edema occasionally complicates both the oral and the intravenous administration of iodids. Localized edema may involve one eyelid without further symptoms of iodism. If this appears, it is best to discontinue the drug.

NON-SPECIFIC TREATMENT OF SYPHILIS

From time to time entirely non-specific agents have been employed in the treatment of syphilis with a view to securing a general or systemic resistance against the disease. Most of these procedures have involved the induction of fever by the injection of tuberculin or other foreign proteins. Their value is as yet undetermined.

THE RATIONALE OF THE COMBINED TREATMENT WITH ARSPHENAMIN AND MERCURY

From the foregoing summaries of the therapeutic action of arsphenamin and mercury, it may easily be seen that both drugs must be used in the treatment of the large majority of cases. If a markedly spirillicidal treatment is important, as in early syphilis, the arsphenamin phase will assume special intensity. On the other hand, it is never safe to trust purely to the spirillicidal virtues of arsphenamin, particularly in the earlier stages of the disease when the organisms are actively reproducing and of maximal virulence. Inasmuch as a spirillicidal arsphenamin technic not only does not build antibodies for resistance, but may leave the patient actually impoverished in this regard, the administration of mercury early in the disease should begin before the close of the arsphenamin phase. It should be continued throughout the rest interval between arsphenamin courses and should overlap into the spirillicidal phase represented by the succeeding arsphenamin course. Only in this way can the patient be kept under the influence of an immunity-building as well as an organism-destroying therapy.

Whenever a syphilitic infection involves an acute phase in an important and already damaged structure, it is a general principle that treatment should not begin with arsphenamin but that for a variable period the slower approach represented by mercury should be employed. This mercurial preparation avoids at least a part of the Jarisch-Herxheimer reaction. The length of this preliminary mercurialization varies greatly, from a week to two in moderate grades of meningeal neurosyphilis, to many weeks or months in the treatment of hepatic and cardiovascular syphilis. A soluble mercurial salt intramuscularly, if the patient's general condition does not contra-indicate, is one of the most rapid and effective methods. Inunctions are relatively slow, and not less than twenty to forty should be regarded as essential to a good preparation. Mercury by mouth should not be included among the methods of mercurial preparation except in conjunction with inunctions. The arsphenamin phase of the treatment of late syphilis must, I believe, lean more decidedly towards moderate doses and resistance-stimulating effects. In early syphilis the patient should be kept constantly under the influence of one or the other drug for at least a year, but in late syphilis the interim periods of four or more months between arsphenamin courses should consist of alternating complete rest and moderate mercurialization by inunctions or intramuscular injections.

Considerable difference of opinion exists among various observers as to the desirability of employing arsphenamin and mercury simultaneously, rather than in alternation. Personally, I have always been an advocate of the simultaneous use of the two drugs whenever possible. I believe there is a definite synergistic action, and that the patient is thus assured of both the protection ascribable to a stimulated resistance and the good effects of spirillicidal action. Wechselmann, and later Eicke, objected to this mode of treatment on the ground that it produced serious effects on the kidney, but in a number of years experience with it I have seen little or no clinical evidence of this. Schamberg has suggested that the combined use of arsphenamin and mercury interferes with the elimination of arsenic, with an increase of arsenical complications. A careful study of this question in connection with the incidence of exfoliative dermatitis on the service of the Section on Dermatology in the Mayo Clinic has failed to demonstrate any such relation. The incidence of this distinctively arsenical complication is no higher on this service than on that of the Johns Hopkins Hospital in which the two drugs are used alternately.

Whenever, therefore, the patient is not hampered by definite contraindications, I believe that the simultaneous use of mercury and arsphenamin is the most satisfactory way to secure really vigorous treatment.

COLLATERAL ELEMENTS IN TREATMENT

The treatment of any syphilitic infection involves a number of factors besides the mere technic of the use of arsphenamin and mercury and the iodids. These factors will be taken up under: (1) appraisal of the defense mechanism and the decision when to treat and when not to treat; (2) the general hygiene of the syphilitic patient including syphilis and marriage; (3) personal hygiene; (4) the effect of treatment on the general status of the patient; (5) focal and intercurrent infections and urinary retention; (6) mental state of the patient; and (7) therapeutic controls in syphilis.

Appraisal of the Defense Mechanism and the Decision When and When Not to Treat

In the early stages of syphilis, the problem of the physician confronted with an active syphilitic infection is a simple one. Treatment is morally and medically obligatory, and the fullest resources of modern methods should be vigorously employed in an effort to suppress the infection at its onset. On the other hand, the decision whether or not to begin treatment in latency, and how far to carry treatment in any type of case, is more difficult and can hardly, in our present state of knowledge, be made the subject of definite rules. However, one general, guiding principle may be indicated: aim to treat the majority of patients well beyond the disappearance of all active symptoms and signs of the disease, if it can be done without demonstrable ill effects. This includes not alone the disappearance of visible lesions, but complete serologic negativity on blood and spinal fluids. In carrying out this plan, be careful to distinguish between active lesions and residua or scars, and do not expect to treat a tabetic until he recovers his knee jerks, or until his pupils again become mobile to light.

At times the decision as to what represents active process and what represents ineradicable residuum is very difficult. The positive blood Wassermann reaction was for some time accepted as a symptom of activity. Until it became negative, and stayed so, the patient was considered actively syphilitic. A reaction against this point of view developed, sometimes even to extremes. A positive blood Wassermann reaction in the late stages of the disease may be a matter of no moment in a certain proportion of cases. On the other hand, a careful investigation of patients whose positive blood Wassermann reaction appears to persist as a scar, so to speak, does not always reassure one as to the benign nature of the syphilis. It is best, therefore, to leave the matter undetermined for the present, and to grant that the fixed or resistant positive blood Wassermann reaction may be a matter of no consequence, but that its lack of consequence can only be established by painstaking and complete examination of the patient from every standpoint and by observation throughout a period of years.

In the appraisal of the patient's status before beginning treatment, age and time factors must be carefully considered. A recently acquired infection in a man between fifty and seventy years of age demands vigorous treatment, for the protection of the social order even more than for the cure of the patient. An infection of long standing, dating back from twenty to forty years, in a patient of from fifty to seventy, on the other hand, demands very little if any treatment. The long duration of the infection in the latter case has done away with the risk of transmission, and preservation of the patient's health through so long a period of years without signs of permanent damage has fairly established the ability of his defense mechanism to take care of him for his few remaining years. It would, therefore, be folly to intervene. The obverse side of the picture is that of the patient in the thirties or forties with a previously untreated syphilitic infection, apparently symptomatically latent although still with a positive Wassermann reaction on the blood. Such a patient should practically never, in my opinion, be left to his unaided defense mechanism, no matter how well he may seem to be. He has too many years in which to develop aortic and myocardial lesions, chronic vascular changes in the central nervous system, gummatous infiltrations in the larger viscera, to make it justifiable to allow him to run his course. Our means of detecting potentially serious changes in these structures are too crude to justify leaving the future entirely to clinical observation. The first symptom detected may be an attack of angina pectoris, or the physical signs of a well-marked aortitis, an optic neuroretinitis or gumma of the stomach. Even the repetition of the general examination and the Wassermann reaction on the spinal fluid does not necessarily disclose all the changes which may go on in this patient as the result of forced reliance on his inflammatory defense. For this reason, patients under fifty years of age should, in general, be given moderate and fairly prolonged treatment, in inverse proportion to the duration of the infection. The shorter the duration, the more vigorous the treatment.

When the patient with a definite and satisfactory history of syphilitic infection and desultory or apparently inadequate treatment has become symptomatically and serologically negative in every particular, what course shall we pursue? Shall we, after one or two years lapse in treatment, attempt to make up for this patient's earlier lacks, even though he is serologically and clinically normal? In cases of this type, I have inclined more and more to decide against further treatment and in favor of observation. At times it is difficult to prove that these patients have had syphilis. After all, what constitutes adequate treatment? It is treatment sufficient to stop the transmission of the disease and cause the permanent suppression of all its manifestations. In some cases it may even be contended that the first one or two arsphenamin injections accomplish the entire result.

Patients who have had fair treatment and who are apparently normal at least two years after all treatment has been discontinued are, in my opinion, legitimate candidates for observation. If the treatment has been definitely inadequate they should be serologically positive or show detectable relapse, especially in the skin and nervous system. If the treatment has been more nearly adequate, it is not likely that the patients will develop manifestations without serologic or symptomatic warning of the recurrent type which will permit the detection of their relapse. In making this decision to observe, rather than to treat an inadequately treated case, much emphasis should be placed on the time elements in the situation. The tendency toward spontaneous Wassermann negativity on the blood becomes more and more marked after the first two years of the disease. The patient whose infection is of more than five years' duration, and whose treatment has been grossly inadequate, needs most careful investigation for signs of activity and may better be treated on general principles rather than left to observation. On the other hand, a patient who has shown no manifestations of relapse for two or three years in an infection of less than five years' duration is more likely to be cured.

The amount of space which it requires to deal with these provisos illustrates very well how much the factor of judgment in the individual case must determine therapeutic decisions. No rule can be accepted as universally applicable.

The existence of positive contra-indications to treatment must, of course, always be reckoned with. A patient with a probable malignancy which is practically certain to cause his death before the syphilitic infection can overtake him should be treated only with a view to increasing his general symptomatic well-being. Active pulmonary tuberculosis, in general, takes precedence over syphilis in treatment, unless the activity of the syphilis directly endangers the patient's contacts. On the other hand, it must not be forgotten that judicious treatment even for latent syphilis, particularly with arsphenamin, after the fever has subsided, may favorably influence the course of tuberculosis by controlling the complicating syphilis. Syphilitic infection appearing in the course of other constitutional conditions, such as pernicious anemia, diabetes, exophthalmic goiter, and so forth, may have to be treated within the limits of tolerance imposed by the general condition. Goiter may reduce tolerance of arsphenamin and interdict iodid. On the other hand, there could be nothing more inexcusable than to forget the complicating syphilis, or to regard it as a triviality merely because for the moment it is overshadowed by another and more acute condition. Cases of this type constitute the medical scandals of syphilologic practice and are all too numerous. To see a case of epithelioma of the tongue, in which the Wassermann reaction is positive, operatively cured, only to develop an enormous aneurysm ten years later because his syphilis, although recognized at operation, was regarded as inactive or a matter of small moment, is to witness the overshadowing of syphilis by surgery. To see the gastric crises of tabes dorsalis appear a decade after the recognition and ignoring of syphilis as a complication of exophthalmic goiter, is to witness the complete defeat of preventive medicine with respect to syphilis.

General Hygiene of the Syphilitic Patient

Every syphilitic patient should have explained to him at the outset in easily understandable terms the mechanism of transmission of his disease. He should be impressed with the following points:

1. The ability to transmit the disease is greatest in early years. After the fifth year, the risk of transmission diminishes in the majority of cases to the point at which it is almost negligible. The patient must be told that his individual case may present variations which invalidate this rule (mucous relapsing type).

2. Treatment controls the infectiousness of the disease, but it does not necessarily guarantee non-infectiousness except immediately after an arsphenamin injection. It is a matter for question whether it is advisable to give the average patient any impression that modern treatment can shorten the five-year-rule regarding infectiousness. While there can be no doubt that it does so in a considerable proportion of cases, the occasions when it fails to do so are very apt to be the most tragic imaginable.

3. Syphilis is transmitted by moist and intimate contacts; kissing and sexual relations are therefore the ideal means of transmitting the organism from person to person. The patient who has had syphilis should absolutely abandon kissing, especially on the lips. Sexual intercourse should be regulated by consultation with the physician and must depend on the make-up and course of the case. In general, the unmarried should abstain from sexual relations through a period of three, preferably five, years after the onset of the disease. Sexual relations between husband and wife should be limited to the time during which the patient is actively under treatment with arsphenamin and should be surrounded with protective precautions during the probationary period, in which relapse is being watched for. The possibility that the semen itself may be infectious, as demonstrated by Eberson, must be borne in mind in the use of protective measures.

4. The patient must be vigorously impressed with the fact that all lesions on or about the mucous membranes, the genitalia and the anus must be regarded as suspicious. This applies to aphthous erosions, hemorrhoids,

and the like, as well as to the more suspicious mucous and hypertrophic lesions. The patient should be shown how to look for such recurrent lesions, and be told to assist the physician in their detection. The risk of producing a syphilophobia in this way may be borne in mind, but in general the coöperation of the patient is so necessary to the detection of relapse that systematic education on this point justifies itself.

5. The infection is transmissible by moist articles of personal use. For this reason the patient should be warned not to use public drinking cups and should be persuaded, so far as possible, to use only his own dishes and towels. Pipe stems, razors and the like should be strictly for his individual use. All dressings from active lesions should be burned, and the patient should sleep alone.

6. The importance of irritants in the production of infectious recurrence is a matter of great moment in the active stage of syphilis. Tobacco is particularly responsible for a type of irritation which seems to favor mucous recurrence in the mouth and throat. For this reason, every syphilitic person should be instructed to give up the use of tobacco. Chronic sources of irritation, such as carious teeth, bad hygiene of the genitalia, irritation from frequent intercourse, discharges from urethral and cervical diseases, may all contribute to the development of syphilitic hypertrophic lesions, erosions, and so forth.

7. Secrecy is one of the fetishes of the medical profession with respect to syphilis. Granted that the gradual remaking of public opinion now in progress with reference to the stigma of syphilis has not yet reached the point at which the patient can announce his infection from the housetops or discuss it in his club, the fact remains that the ethical and public health obligations involved demand that at least one person be fully informed as to the nature of the situation. This person is the husband, wife, or extramarital sexual partner. The risks to which the uninformed marital partner is exposed by the active syphilitic are so serious that there can be no possible justification for the conspiracy of outrageous silence which constitutes one of the lamentable traditions of an older syphilology. If the tactful physician will give the infected patient the benefit of any doubt which may exist, and will pass over, avoid, or explain in a humane spirit the fact of infection, in his interview with the partner, he will practically never bring about a rupture between husband and wife. In my entire professional experience with syphilis, I have rigidly maintained this stand, and I have in that entire experience seen only one case in which the husband, already seeking an opportunity to leave his wife, took advantage of the situation. Women practically never make the fair-minded and open explanation of a syphilitic infection in their husbands a ground for separation, providing they can feel assured of the physician's coöperation in protecting them, and the husband's full willingness to meet his obligations in the case. It is much better for the husband or the wife to meet any situa-

tion created by an honorable frankness, than for the physician to become an accessory before the fact in the committing of a medical crime.

Syphilis and Marriage.—The question of the marriage of the patient with syphilis involves two phases: (1) the transmission of the disease to the marital partner and children by the intimate contacts of family life; and (2) the question of economic fitness to meet the responsibilities of marriage. Of the two, the former is much the more serious, and it is much more difficult to obtain the patient's coöperation in its adjustment. It is a comparatively simple matter to postulate a safe rule for the marriage of the patient with syphilis. The experience of the older syphilographers, notably Fournier, who gave this question much attention, gradually lengthened the time of probation from two or three years after infection to an almost indefinite period in cases in which there was a marked tendency to recurrence. Keyes, in an often quoted study of his experience in private practice, was able to substantiate the general belief that the risk of infecting the wife becomes very small after the fifth year from the date of the husband's infection. Hoffman's rule has always seemed to me a fairly satisfactory compromise from the theoretic side. Three years of vigorous treatment, with not less than three full courses of arsphenamin the first year and two more years of mercury by an effective method, followed by two years of absolute freedom from recurrence serologically and clinically (including the spinal fluid examination), makes as good a standard as is now available for the fitness for marriage of the patient with syphilis. The question as to whether this period of observation should be shortened by the intensive use of modern treatment methods depends to some extent on the methods. I believe, in the face of long experience with the clinical behavior of the disease, that it is distinctly unwise to let down the theoretic bars. In fact, the distinct predisposition to relapse which one observes following the average ineffective modern treatment of syphilis is a cogent reason for maintaining the standard of observation rather than for reducing it (Figs. 3, 4, Case 2).

We now confront the question of the practicability of enforcing a five-year standard. My experience has not precisely encouraged enthusiasm on this point. In spite of the assistance of the newly developed state venereal disease control legislation, and in spite of all the resources in personal influence which it is possible to bring to bear, all but the most conscientious of patients do pretty much as they please in the matter of marriage, once their obvious symptoms have disappeared and their blood Wassermann reaction has become negative. For this reason I feel that, while we should urge the theoretic standard on all who can be induced to accept it, it is wiser to try to win the coöperation of the less responsible patient by inducing him to have his fiancée meet the physician for a frank discussion of the situation, and then to permit marriage under therapeutic control and precautionary measures. If husband and wife are carefully enough educated to the situation by the physician, a period of two or three years of probation, while the carrier of the infection is passing out of the theoretically infectious stage, can be lived through without infection of the partner and without risk of infected pregnancies. In the main, I believe that this modified procedure, carefully carried out, may offer more than the clandestine sexual life and intercourse with prostitutes which the lax patient with syphilis is likely to substitute for the marital relation which is forbidden him.

The problem presented by an acute syphilis in marriage is fortunately at the present time very much simplified by the availability of arsphenamin. There can be no possible excuse for delaying the use of the drug in an acute syphilis unless the patient can be isolated on a hospital service while a slower preparatory treatment is in progress. The patient should be explicitly told that his period of mercurialization is the least protected from the standpoint of infectiousness, and that, while he may have intercourse during the arsphenamin phase, sexual relations should be discontinued entirely during the mercury interim, at least until after the first eight months or a year of treatment. Protective measures should invariably be used and the infected person and his marital partner strictly enjoined against kissing and other intimate contacts, and to the use of separate dishes, sleeping apart and the like. In general, I believe that it is sound policy not to accept the Wassermann reaction alone as a guide to marriageability any more than as an indication of cure. There is no question but that properly treated patients with persistent positive blood Wassermann reactions may be entirely non-infectious and capable of becoming healthy parents. On the other hand, the finding of a positive blood Wassermann reaction should always make one pause in commending the patient for marriage and should be the signal for the most careful search for signs of activity. No untreated syphilitic person with positive blood Wassermann reaction should be permitted to consider marriage. The minimal amount of treatment which might make him eligible, all other circumstances considered, should be at least three full arsphenamin courses with interim mercurialization approximating 300 inunctions carried over a period of two or three years.

The problem of the woman with syphilis is in some respects more serious from the standpoint of marriage than that of the man. While it has been shown that the semen of latency may produce syphilitic infections, it is even clearer that a woman may appear to have undergone an almost complete symptomatic arrest of her syphilitic infection and yet sustain an infected pregnancy. This fact has led to the suggestion that all women who have had syphilis, irrespective of the stage or character of the disease and the amount and kind of previous treatment, should receive treatment in preparation for and during each pregnancy in order to protect the child. The increasingly encouraging results of antenatal treatment in clinics dealing with syphilitic pregnant women seems to justify this as prophylaxis. The uncertainty surrounding the status of paternal transmission has led to what would seem to be the equally reasonable suggestion that the husband who has had syphilis, if he can be induced to do so and the matter can be planned, should take treatment for his syphilitic infection before conception is allowed to take place, even though there may be no active signs of the disease. Both these points of view would seem to be especially applicable in the management of the early case. The possibility of infection of a pregnant mother by a seemingly latent husband must be remembered.

The question of the social fitness of the syphilitic patient for marriage from the standpoint of his ability to meet the responsibilities entailed by a wife and children must be decided in each individual case, and no blanket permission should be given to any patient who presents evidence of involvement of the nervous system, of the heart, or a tendency to infectious relapse. This will practically eliminate from definite assurances about 25 per cent of early syphilis as seen in the ordinary clinic, for there can be no possible excuse for authorizing the marriage of the patient who shows definite signs of early neurosyphilis, even though mild, until he has recovered under the fullest requirements of treatment and passed at least three years of observation. Such a patient may find himself in the situation of having more to handle from the standpoint of his own ailment than he can successfully negotiate, to say nothing of assuming responsibility for the welfare of a wife. In the later stages of syphilis the same cautions apply. Even though the active syphilitic process has been brought to a stage of arrest, *the prospective marital partner should know the risks involved before and not after marriage takes place.* These risks are best explained by the physician if the patient can be induced to accept his mediation with the prospective partner.

Syphilis and the Family.—One of the most important contributions to modern syphilology has been the demonstration that syphilis in the patient means syphilis in his familial contacts. Solomon and Solomon in their investigation of 555 family groups with the assistance of the Interdepartmental Social Hygiene Board found that only 33.3 per cent, or less than one-third, should be considered as definitely free from syphilis, or defects possibly due to syphilis. At least one-third of the families of syphilitics have one or more syphilitic members besides the original patient. Between one-third and one-fourth have never given birth to a living child, while one-tenth is the accepted incidence of sterility in families taken at large. It is worth while to quote literally these authors' entire summary as the best propaganda material available in dealing with the syphilitic patient himself and with those whose coöperation must be obtained in following to its source the trail of syphilis in the family.

"1. The family of the late syphilitic abounds with evidence of syphilitic damage.

"2. At least one-fifth of the families of syphilitics have one or more syphilitic members in addition to the original patient.

"3. Between one-third and one-fourth of the families of syphilitics have never given birth to a living child. This is much larger than the percentage obtained from the study of a large group of New England families taken at random. Here it is shown that only one-tenth were childless.

"4. More than one-third of the families of syphilitics have accidents to pregnancies, namely, abortions, miscarriages, or stillbirths.

"5. The birth-rate in syphilitic families is 2.05 per family; whereas the birth-rate in the New England families mentioned above is 3.8 per family or almost twice as high.

"6. Over one-half of the families show defects as to children (sterility, accidents to pregnancies, and syphilitic children).

"7. Only one-third of the families show no defect as to children or Wassermann reaction in spouse.

"8. About one-fifth of the individuals examined show a positive Wassermann reaction; more of these are spouses than children.

"9. Between one-fourth and one-third of the spouses examined show syphilitic involvement.

"10. Between one in twelve and one in six of the children examined show syphilitic involvement.

"11. One-fifth of all children born alive in syphilitic families were dead at the time the families were examined. This does not differ materially from the general average in the community.

"12. One-fifth of the pregnancies are abortions, miscarriages, or stillbirths, as compared with less than one-tenth of the pregnancies in non-syphilitic families.

"13. The average number of pregnancies per family is 2.58 compared with 3.88, 4.43, and 5.51 in non-syphilitic families.

"14. There are 3.52 stillbirths per 100 live births in the syphilitic families, as compared with the 3.79 reported by the Massachusetts Census study of non-syphilitic families. This shows no very marked difference.

"15. A syphilitic is a syphilitic, whether his disease is general paresis, cerebrospinal syphilis, or visceral syphilis without involvement of the central nervous system, and the problems affecting his family are the same in any case."

The problem of the private physician in dealing with familial follow-up is unquestionably much more difficult than that of the institution, clinic, or center. Yet it is impossible to escape the fact that a preventive outlook on the disease must insist on bringing under treatment, provided treatment is indicated, every person with syphilis who can be discovered.

The individual physician unquestionably can do a good deal more than he has ever felt called on to do. The average patient of a pay clientele type, when the situation is dispassionately and considerately explained to him, is eager to secure the examination of his family and contacts. This examination takes one at once into the problem of heredosyphilis, which is in many respects distinctly more difficult of diagnosis than that of the acquired form of the disease, and not to be settled merely by Wassermann tests. None the less it is decidedly worth the effort to make a thorough investigation, and no physician can feel that he is carrying on along modern syphilologic lines who does not take this responsibility seriously to heart. It is possible, by invoking the assistance of a consultant and a diagnostic center of treatment, or the social service divisions of the State Boards of Health, to secure coöperation which the individual physician cannot obtain alone.

To what extent can the average syphilitic patient be relied on to meet the requirements of individual hygiene with respect to others? This, like the problem of inunctions, is to no small extent a function of the physician's personality. He who handles his syphilitic patients perfunctorily and with reluctance, whose outlook on the disease is cynical, and who is too busy to individualize the situation, will not inspire the patient to effective coöperation. Most patients in a private clientele have an arousable conscience. For the irresponsible the assistance of the State Board of Health provides coercion. For the ignorant it provides literature concerning the facts, if prolonged conversations are impossible. The invoking of the prestige and equipment of a syphilologic center or consultant to assist in making the necessary impression aids in simplifying the situation for the general practitioner if he will use them. Certain patients unquestionably will not coöperate. For these, arsphenamin therapy pushed to the limit, and public health control even to the extent of placarding and isolation with treatment, is as yet of undetermined efficacy. Whether or not these extreme measures should be invoked should be left optional with the physician or expert, and not made a blanket provision of the law to be used indiscriminately against the conscientious and the indifferent alike.

PERSONAL HYGIENE OF THE SYPHILITIC PATIENT

Trauma and Overstrain.—There is as yet a distinctly intangible element in the problem of creating resistance to syphilis by methods other than specific treatment. On the one hand, one sees patients of the most robust physical and nervous make-up carried off by the worst complications of the disease. On the other hand one sees, in startling contrast, men and women who have "gone the ropes" in every species of indiscretion and dissipation, and yet whose syphilitic infections run a benign course, responsive to insignificant treatment. It is a general impression that the maintenance of good health and the avoidance of debilitating influences favorably affects the course of syphilis in the individual patient. Trauma has been shown repeatedly, by its establishment of a point of lowered resistance, directly to favor the appearance of a late syphilitic lesion. Trauma is especially influential in the development of bone lesions, and particularly of the tabetic arthropathies. Every tabetic should be warned against the danger of Charcot joint following a sprained ankle, wrenched knee, and so forth. Nervous overstrain has seemed to me to predispose to some extent to active neurosyphilis. Intercurrent infections, such as influenza, also predispose to the advance of a neurosyphilitic process. All patients with syphilis should therefore be carefully instructed, especially in the later years of their infection, to protect themselves from these three types of influence. It should be recalled, in connection with nervous overstrain, that the worry and introspection incident on idleness are often more serious menaces to mental health than a considerable pressure of absorbing and interesting affairs.

The influence of cold and wet in predisposing to infections should be borne in mind and in late cases patients who can do so should, if possible, seek mild winter climates. On the other hand, it must never be imagined that attention to these points is a substitute for specific treatment.

Rest.—Rest has a general non-specific value in the management of certain aspects of syphilis, such as cardiovascular lesions. Requirements in this respect should not be made extreme. Rest in bed is rarely required in the control of syphilis. On the other hand, ability to relax, if it can be accompanied by the ability to forget or by restoration of hope and confidence, is an important therapeutic aid. In general, syphilitic patients should be instructed to keep regular hours and get at least eight hours of sleep at night.

Weight.—The weight is a valuable index of progress. The general tendency of patients under treatment is to gain. The gain in weight is, of course, more pronounced if the lesion has interfered with taking food, as for instance in cases of gummatous ulcers of the pharynx or tongue, or lesions of the stomach and esophagus. In such cases the gain in weight under the quick symptomatic results of arsphenamin treatment is immediate and often astounding. More patients, however, register their maximal gain during rest intervals, and this constitutes another of the many arguments in favor of intermittent treatment. While the patient does not need to watch his weight with the care customary in tuberculosis, a distinct drop in weight should always be interpreted as a warning, and call for a rechecking of the patient's clinical and serologic condition. On the other hand, mere gain in weight is not always an advantage, as for example in cardiovascular lesions and hepatic cirrhosis in which it may produce further strain on a weakened heart, or represent accumulations of intra-abdominal fluid.

Diet.—The diet of the syphilitic patient must be modified to meet his individual situation, and the physician should make his advice on this point specific and applicable. During the administration of mercury, it is my custom to employ an acid-free diet for the prevention of stomatitis. In general, the patients should tend towards an abundant or forced diet, with a view to bringing about a gain in weight. The proportion of coarse foods should depend somewhat on whether treatment has a constipating or a laxative effect. Regulation of the bowels is so important in making a course of treatment run smoothly that this matter should have special attention, and water before breakfast, prunes and figs, medicinal bran and the use of a mild alkaline laxative should be given particular attention. The chronic intestinal atony of tabetics is especially trying at times and may be relieved to some extent by the use of the medicine ball (8 to 12-pound iron shot) rolled over the abdomen, or by rectal injections of 2 to 3 ounces of olive oil every evening to be retained; this in addition to the use of liquid petrolatum by mouth. The presence of an active duodenal or gastric ulcer is a contra-indication to some of these measures.

Renal Irritation.—Patients who show signs of pronounced renal irritation should be instructed to avoid condiments, spices and seasonings and the hot and peppery vegetables such as onions, radishes and the like. Depending on the degree of renal irritation, we have found it advisable to reduce the protein intake at times, even to the point of completely eliminating meat, although the patient may have one or two eggs daily. A modified low protein diet allows the patient a lamb chop and one piece of chicken each week.

Alcohol and Other Stimulants.—The reaction of the syphilitic patient to alcohol varies a good deal in different cases. The weight of tradition is distinctly against permitting patients with syphilis to use alcohol in any form. Personally, I have found it essential to be too insistent on this point, rather than to make too many exceptions. The use of alcohol, especially if carried to the point of abuse, makes the patient irresponsible and difficult to control precisely at times when control is most important. Used in any considerable quantity, its ability to lower the resistance of the nervous system seems to be generally conceded.

Other stimulants, such as caffein, should be used with discretion by the syphilitic patient. Regular sleep and a minimum of irritability are of service in managing any constitutional ailment, and should be striven for in treating syphilis. On the other hand, there can be no object in indulging in therapeutic asceticism and making the patient wretched with prohibitions that are essentially of small moment.

The use of tobacco in the later years of a syphilitic infection involves no special principles other than those of medical management. It is in the earlier years of syphilis that tobacco as an irritant produces mucous recurrences and paves the way for subsequent leukoplakia and carcinomatous accidents. For the patients with repeated mucous relapses, it must be absolutely forbidden.

Effect of Treatment on the General Status of the Patient

In early syphilis, the flare-up produced by modern intensive treatment is of very short duration, and the rapid disappearance of symptoms of the disease is accompanied by a general increase in the patient's well-being. However, as the disease becomes more deep rooted and debilitating, and the constitutional effects more pronounced, the Herxheimerlike exacerbation of symptoms becomes longer and in the first two or three weeks of the first course of treatment a marked and puzzling increase in the number and variety of the patient's complaints may be noted. These complaints may be accompanied by actual objective changes, such as edema and inflammatory reaction in the involved structure, by a rise in cell count of the spinal fluid in neurosyphilis, or the appearance of pulsation in an aneurysm previously quiescent. Bone lesions, in my experience, have been particularly slow in passing through this phase of local reaction, and several weeks after treatment has begun may actually be markedly worse than before. The Herxheimer reaction even extends to paresis, so that it is a not uncommon occurrence for patients, when first placed under treatment, to go through an exacerbation of mental symptoms which may necessitate putting them temporarily in restraint. Showers of lightning pains and even a gastric crisis may mark this first phase of reaction to effective treatment in tabetics.

In late cases, the symptoms of which the patient complains begin to subside about the third or fourth week, and this general improvement continues throughout the remainder of a well-managed course and well on into the subsequent interim. In fact, many of the best effects of treatment in all types of cases do not become manifest until the rest period which should follow an intensive course. The weight may have remained stationary for the entire period of active treatment only to increase rapidly to an almost miraculous degree in the ensuing month. I have noted a gain of 100 pounds in four months in a case of gastric syphilis. When a patient who is markedly below par fails to make a substantial gain in the interim between two courses, a most painstaking search for all collateral, retarding factors in the case should be made. Teeth should be X-rayed, tonsils examined, habits of living and diet inquired into, and the state of mind carefully canvassed for anxieties and worries. If nothing can be found to explain the situation, the possibility of overintensive treatment should be thought of. The overtreatment syndrome varies somewhat with the type of treatment. Patients who have been on prolonged or excessive mercurial treatment are usually depressed and pale, unenergetic, and somewhat anemic. Stiffness, aching and malaise are common complaints. Patients who have been pushed too hard with arsphenamin exhibit a heightened nervous irritability amounting at times almost to hysteria. Depression alternates with excitement and emotionalism. In either type, discontinuance of treatment with reassurance is essential. The physician should not be too easily led to make a diagnosis of an overtreatment syndrome in patients who, on a little careful analysis, can easily be shown to have an unfavorable physical condition or a mental state or problem underlying their reactions.

Focal and Intercurrent Infection and Urinary Retention

Among the important depressing and unfavorable influences in the course of syphilis, emphasis must be placed on complicating infections, especially of the chronic type. An acute infection may at times, especially as in the case of influenza, act as the starting point for accidents such as myelitis, spastic paraplegia, deafness, interstitial keratitis, and the like. The influence of the chronic infection is more subtle but none the less analyzable in individual cases. Its influence on the renal tolerance of medication has been mentioned. A general anasarca, getting progressively worse under treatment of a diffuse hepatitis, may rapidly subside on the removal of a mouthful of apically infected teeth. Tabetic lightning pains and gastric crises may be markedly bettered and at times cleared up entirely by extirpation of focal infections. The fact that such improvement may take place without the assistance of active antisyphilitic treatment is evidence of the influence of the defense mechanism and of general resistance on the course of syphilis. While early cases of syphilis seldom present such definite indications for the removal of foci as do many late cases, the prophylactically minded physician will accept their influence as established and diminish the patient's background for complications by urging the clearing up of all collateral infective factors as early as possible.

Urinary retention and secondary infection is an extremely important element in keeping tabetics below par. In fact, the change which some cases undergo for the better is at times as much the result of the restoration of urinary output by systematic emptying of the bladder and reduction of the pyelitis and pyelonephritis, as of any medicament. Every tabetic patient should be regarded as potentially uremic, the integrity of his eliminative mechanism thoroughly studied, and any retention and infection corrected. Catheterism should not be prematurely resorted to, but the patient should be taught to evacuate the bladder by posture and effort, if possible. Irrigation of the bladder with boric acid solution is in order when infection is already marked. The blood urea excretion and phenolsulphonephthalein output should be taken from time to time. The odor of urine about a patient, and the history of dribbling either by day or night, usually means a full, atonic, and not an empty, uncontrolled bladder.

MENTAL STATE OF THE SYPHILITIC PATIENT

This element in the care of the patient with syphilis receives all too little attention at the hands of many therapists, yet it is none the less a very real factor in efficient management. The stigma which attaches itself to syphilis has fortunately diminished somewhat in the past few years, but still works its greatest harm where there is the least justification. Flagrantly culpable and indifferent patients are little affected by it. It is always the patient whose syphilis is his misfortune rather than his fault who suffers from the depressing effect of a mistaken social outlook on the disease. Ever-increasing knowledge of syphilis has done good in counteracting the effects of half knowledge, yet all too many patients with syphilis still carry in the background of their minds the conviction that they are lost, that they must never marry, that their wives or children have or will disown them, that they are destined for the insane hospital, or for lingering forms of illness and death. It requires patience and constant reiteration by the physician to rectify these mistaken notions and to convince the patient that he can up and carry on with a good grace in the practical assurance of better than a "fifty-fifty" chance for complete arrest or recovery.

True anxiety complexes must be systematically looked for in every syphilitic patient who shows signs of persistent depression or failure to respond promptly, both physically and mentally, to treatment. The picture may, of course, be due to a cortical vascular degeneration. While it is not wise to throw all caution to the winds in one's prognostication, the outlook for syphilis in general is so good, under proper management, that one is justified in adopting a systematic régime of encouragement in handling conscientious syphilitic patients. The limits of common sense should be respected, however, and no promises of cure made which cannot be thoroughly backed by evidence. The value of an honestly hopeful but clear and conservative statement to the patient cannot be overestimated. The adjustment of family problems and provision for meeting the inquiries of busybodies are also as necessary a part of the successful treatment of syphilis at times as are arsphenamin and mercury.

One is frequently impressed by the striking gain in well-being and business capacity shown by patients who were rather dull, apathetic and slovenly at the time of their examination. In the reverse direction, one occasionally finds surprising deteriorations in mental power and efficiency following what seem to be comparatively trivial lesions, especially of the nervous system. These latter are of the order of Collins' "psychic scar" and probably represent cortical degenerations associated with the involution of vascular lesions showing few clinical or serologic signs. The possibility of unforeseen cortical degenerations must lead one to be a little cautious in giving the prognosis of patients who, without definite evidence of paresis, exhibit signs of mental change before treatment is begun.

Anxiety and mental make-up form a prominent factor in the therapeutic outcome in the cardiovascular types of the disease. These patients, to whom the heart inevitably appeals as the center of their existence, are the victims of a neurosis which at times is even more serious than the organic cardiovascular lesion itself.

THERAPEUTIC CONTROLS IN SYPHILIS

Healing.—Disappearance of lesions and restoration of normal function is, of course, one of the primary aims of treatment. In early syphilis this aim is easily attained but, unless treatment is carried well beyond this symptomatic end, relapse is usually prompt and often serious. Seven to ten days, according to size, is the average healing time of the primary lesion. The induration may persist six weeks, even under effective combined treatment. Macular and follicular cutaneous secondary lesions disappear within a few days; papular lesions may be much more persistent, especially if abundant on the face. Mucous lesions usually disappear within three days, condylomas behave as primary lesions. Rupial or ulcerative secondary syphilids (Figs. 5 and 6) heal in from three to four weeks unless very extensive. Bone lesions may become painless, but if gummatous may be many weeks or months in healing, especially if they are about the skull and face. In six weeks, however, the average bone lesion is much improved.

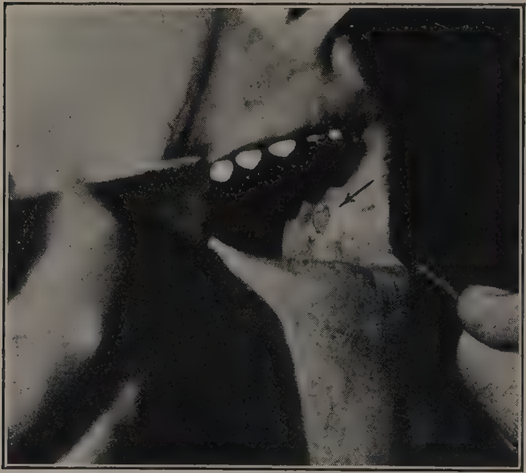


FIG. 3 (CASE 2).—RECURRENCES ON MUCOUS MEMBRANE, IN SPITE OF TREATMENT; BEGINNING LEUKOPLAKIA. Active mucous patch near the left labial commissure, a common site for such lesions.

Secondary fibrosis and scarring may delay healing considerably, as after surgical intervention with extension, in the case of gumma. Overtreatment with the Roentgen ray, and chronic vascular stasis, may greatly delay healing and alter the appearance of syphilitic ulcers of the lower extremities.

Case 2.—These were the only lesions presented by the patient at that time, and they were discovered as a result of what the writer felt to be merely perfunctory examination of the patient before dismissal for a long rest period. The patient, a dentist, had just taken a provocative arsphenamine injection on his own initiative, thinking that this would give sufficient evidence of his condition without further examination. He developed two partial positive reactions in three tests. The spinal fluid was normal. The darkfield was rendered valueless by the arsphenamine provocative injection, which through error was done before examination.

The duration of this infection at the time these photographs were taken was five years and four months, and yet the patient was still actively infectious, and the lesions were of the early recurrent type.

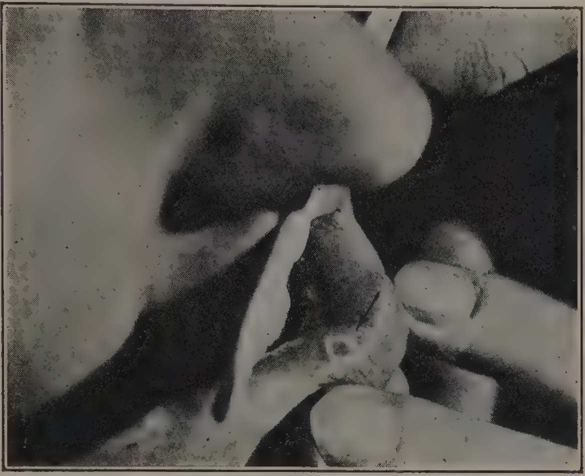


Fig. 4 (Case 2.)—An Involuting Mucous Patch of the Lip in the Same Patient, Entirely Concealed Until the Lip is Everted. A faint silvery leukoplakia is developing around the lesion. The patient's own fingers are controlling the lip, which should not be touched by an examiner with ungloved hands.

The patient had received four injections of arsphenamin with his secondaries five years before, and two provocative procedures, the one three years before being completely negative.

He had had mercury salicylate intramuscularly eight months a year (thirty-two injections, 1 gr. each) for two years, and sixty-five 30-gr. inunctions.

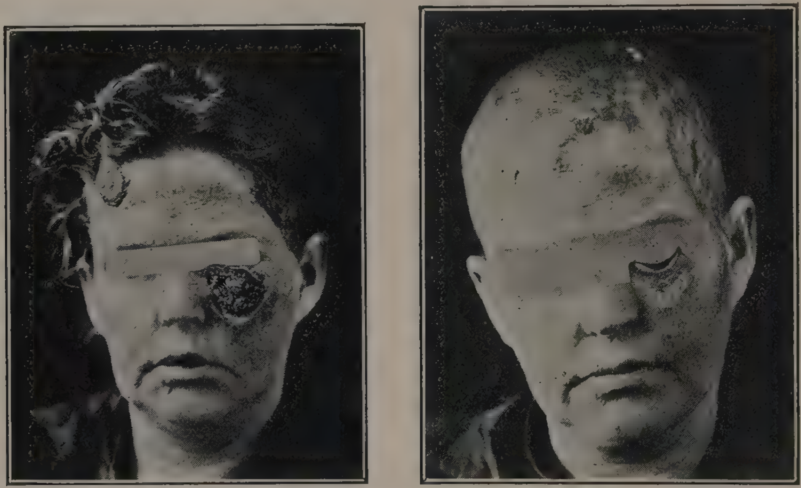
This is typical of the course of many infections as treated in ordinary practice today.

Treated or not, reëxamine all early cases at frequent intervals for infectious lesions, regardless of the Wassermann findings.

Recall that mercury is a poor preventive of recurrences on mucous membranes, and that this patient had had a negative provocative procedure three years before, and only a partial positive Wassermann test at the time these lesions were present.

The proportion of active inflammatory process to scar and degeneration in all deep lesions of syphilis greatly influences the degree of restoration possible. For example, acute neuroretinitis, in spite of the alarming picture it presents ophthalmologically, has a much better outlook for improvement in vision (Case 6, p. 538) than has even a moderate degree of simple primary optic atrophy with its pale disc and relatively unimpressive fundus pathology. Active meningeal neurosyphilis, although it has a high cell count in the spinal fluid, a marked excess of albumin, and so forth, often responds more promptly and permanently than does a later type with a low cell count and a small amount of globulin increase. The degenerative changes which constitute symptomatic advance in the face of a completely negative serology may be the most discouraging of all.

Healing cannot be accepted as evidence of the cure of syphilis, or even of its presence, ipso facto. The non-specific effects of treatment for syphilis are marked enough, as I have indicated in the discussion of the therapeutic test, to make it necessary to invoke all available evidence. A purely symptomatic outlook has therefore no place in modern methods. Treatment must always be carried beyond healing to prevent relapse. At the same time, this prolongation must not be too long or too intense, lest the very immunity reactions which brought about the response be sacrificed to overdoing.



FIGS. 5 and 6.—Therapeutic response of a rupial syphilid to three injections of arsphenamin at weekly intervals.

Therapeutic paradox must be borne in mind in controlling treatment. The syphilitic process in a viscus may get better, while the patient gets worse. This is the result of too rapid or overenthusiastic treatment which does not permit time for adjustment of the treated structure to the new situation. Examples of the therapeutic paradox may be seen especially in hepatic and cardiovascular syphilis. As an aspect of therapeutic paradox, it must be borne in mind that the physical signs by which a lesion was identified may actually become more marked as a result of the changes induced by treatment. For example, the murmur of aortic regurgitation may increase in intensity for a time after treatment is begun, and finally become stationary as a result of the increased distortion and shrinkage of the valves from cicatricial contraction. The resolution of a periaortitis or mediastinitis may cause an aneurysm, previously fixed, to show pulsation grossly and by fluoroscopic examination.

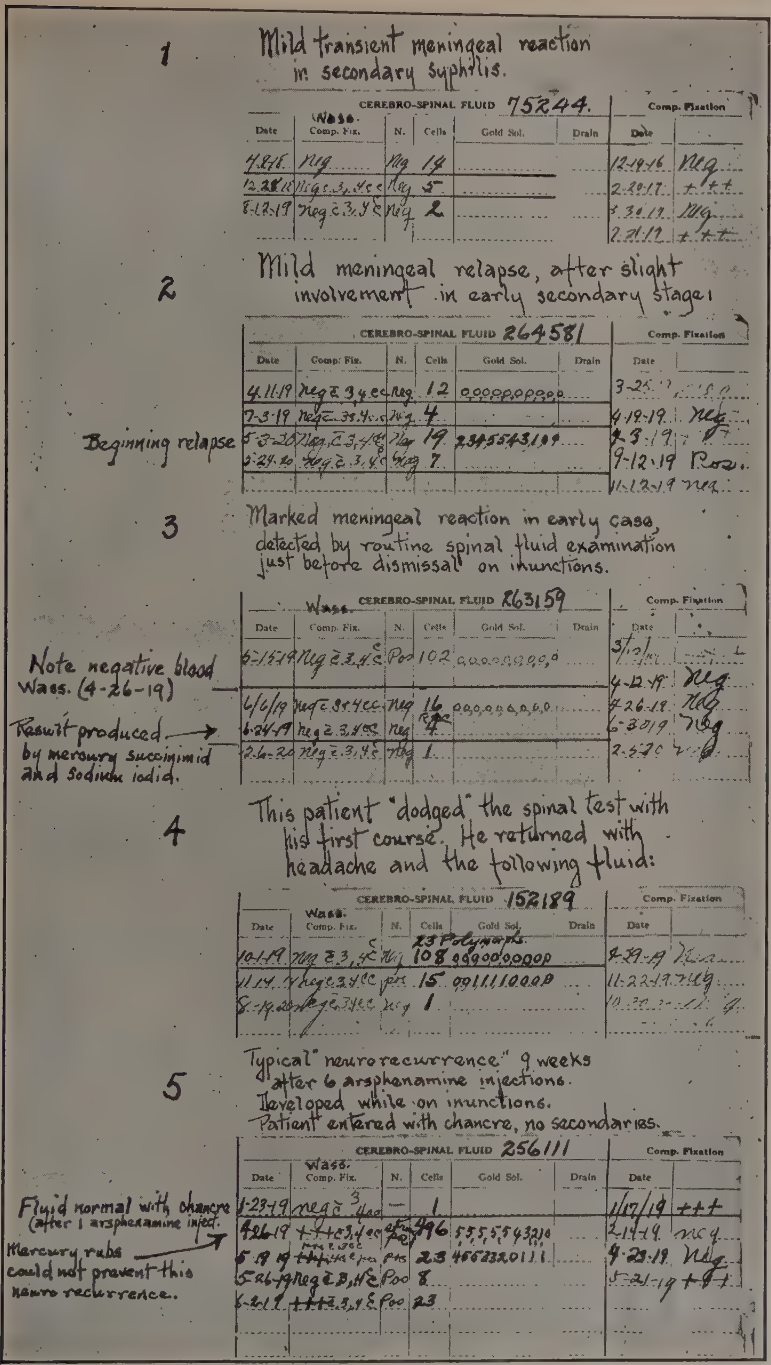
Certain signs and symptoms, which may be regarded as evidence of the degeneration of irreplaceable structures and functions, cannot be used as therapeutic guides. For example, from objective examination by the neurologist it may appear that the patient has shown no improvement under treatment. This is simply because the signs employed are those of degeneration in an irreplaceable tissue. On inquiring subjectively into the patient's story, we find, however, that he feels much better and is relieved of many of the symptoms that accompanied the active inflammatory process, and we may find objectively that his serologic signs have likewise responded. Treatment should not be expected to do the impossible and restore lost knee jerks or unlimber "frozen" pupils.

The Blood Wassermann Reaction.—Precisely as the blood Wassermann reaction is only one symptom of a syphilitic infection, so it is only one element in any system of therapeutic control. Its importance has diminished very considerably with a better comprehension of its possibilities of error. In the early years of a syphilitic infection, repeated negative blood Wassermann reactions are, of course, desirable, and every effort should be made to obtain them. Persistent or fluctuating positive reactions must be explained, and are prima facie evidence of relapse. On the other hand, the negative blood Wassermann reaction alone, repeated ad infinitum, would never prove the cure of a syphilitic infection. Enough patients go on to the condition of neurosyphilis and to advanced degenerative lesions of other types in spite of a negative blood Wassermann reaction to make it unjustifiable to trust even an indefinite repetition of such a finding as evidence of cure.

In the later years of a syphilitic infection in the patient who is young enough to have time for complications, an effort should be made to reverse the positive blood Wassermann reaction to negative and keep it there, precisely as one would endeavor to cause the disappearance of a visible lesion. If the blood Wassermann reaction proves resistant, I believe it should be regarded as presumptive evidence that the patient has a significant visceral lesion, rather than a trivial or insignificant syphilis. Every effort should be made to ferret out the cause for the irreversible positive reaction. Such ferreting should include a special cardiovascular history and examination including electrocardiography and Roentgen ray of the chest, with particular attention to symptoms of coronary sclerosis, to the physical signs of aortitis and aortic dilatation, to hypertension, and to signs of cerebral arteriosclerosis. The osseous system should be carefully searched and tender points and joint abnormalities examined by the Roentgen ray. An effort should be made to palpate the liver and the spleen, and the nervous system should be investigated by examining the spinal fluid and by the objective neurologic examination. An ophthalmoscopic examination of the fundus of the eye should invariably be carried out. If none of these various examinations discloses abnormalities, the resistant positive blood Wassermann reaction may, perhaps, after three courses of treatment, be set aside as ground for observation only, and the patient dismissed from further treatment until definite indications arise. He should not, however, be dismissed from observation and should be reëxamined as often as every year or two, for life, to be sure that nothing develops which demands attention. The spinal fluid examination, if it has been negative two or three times in succession over a period of three or four years, need not be subjected to repeated investigation.

The negative blood Wasserman reaction in late syphilis is meaningless and is practically not a factor in therapeutic decisions. In a patient with syphilis whose blood Wasserman reaction is negative, the effort should be made to meet the symptomatic indication, to secure a maximal restoration of the patient to health and efficiency, and to watch at intervals of a year or two throughout life for signs of relapse.

Spinal Fluid Examination.—Modern syphilology has gained immensely by systematic direct examination of the spinal fluid. This procedure now forms an absolutely necessary part of the therapeutic control of syphilis and the general practitioner cannot assume that he is doing justice to the cases he handles unless he either skillfully performs this test himself, or avails himself of a consultant's assistance in its correct performance and interpretation. By the examination of the spinal fluid, it has been shown that involvement of the nervous system occurs in some degree in as high as 60 per cent of all patients within the first few weeks of the disease. In about 30 per cent the involvement proves to be of a mild type and disappears under ordinary treatment without further attention. On the other hand, in approximately 25 to 30 per cent of all patients, involvement of the nervous system assumes a potentially serious form. The earliest and simplest change is a rise in cell count and increase in globulin, evidencing a meningitis. Later, in the more severe cases, there is a positive Wassermann reaction on the spinal fluid which is detectable only in large amounts of fluid in cases which respond to ordinary measures of treatment, but is strongly positive in small amounts in cases that are likely to prove resistant. It has been the practice in the Section of Dermatology to examine the spinal fluid of all patients with early syphilis routinely within the first two weeks of treatment, and at least two or three times during the ensuing year, to determine the progress of this aspect of the case. From this systematic study it appears that even



1 Mild transient meningeal reaction in secondary syphilis.

CEREBRO-SPINAL FLUID 75244.

Date	Wass. Comp. Fix.	N.	Cells	Gold Sol.	Drain	Comp. Fixation Date	
4.8.16	Neg	Neg	14			12.19.16	Neg
12.28.16	Neg c̄ 3,4 cc	Neg	5			2.20.17	+ ++
8.12.19	Neg c̄ 3,4 c	Neg	2			3.30.17	Neg
						2.21.19	+ ++

2 Mild meningeal relapse, after slight involvement in early secondary stage.

CEREBRO-SPINAL FLUID 264581

Date	Comp. Fix.	N.	Cells	Gold Sol.	Drain	Comp. Fixation Date	
4.11.19	Neg c̄ 3,4 cc	Neg	12	0,0,0,0,0,0,0,0,0,0		3-25-19	[illegible]
7-3-19	Neg c̄ 3,4 cc	Neg	4			4-19-19	Neg
5-3-20	Neg c̄ 3,4 cc	Neg	19	2,3,4,5,5,4,3,1,0,0		7-3-19	[illegible]
5-24-20	Neg c̄ 3,4 cc	Neg	7			9-12-19	Pos.
						11-12-19	Neg

Beginning relapse

3 Marked meningeal reaction in early case, detected by routine spinal fluid examination just before dismissal on inunctions.

CEREBRO-SPINAL FLUID 263159

Date	Wass. Comp. Fix.	N.	Cells	Gold Sol.	Drain	Comp. Fixation Date	
6-15-19	Neg c̄ 3,4 cc	Pos	102	0,0,0,0,0,0,0,0,0,0		3/12/19	[illegible]
						4-12-19	Neg
6/6/19	Neg c̄ 3+4 cc	Neg	16	0,0,0,0,0,0,0,0,0,0		4-26-19	Neg
6-24-19	Neg c̄ 3,4 cc	Neg	4			6-30-19	Neg
2-6-20	Neg c̄ 3,4 cc	Neg	1			2-5-20	[illegible]

Note negative blood Wass. (4-26-19)

Result produced by mercury succinimid and sodium iodid.

4 This patient "dodged" the spinal test with his first course. He returned with headache and the following fluid:

CEREBRO-SPINAL FLUID 152189

Date	Wass. Comp. Fix.	N.	Cells	Gold Sol.	Drain	Comp. Fixation Date	
10-1-19	Neg c̄ 3,4 cc	Neg	23 Polymorphs. 108	0,0,0,0,0,0,0,0,0,0		4-29-19	[illegible]
11-14-19	Neg c̄ 3,4 cc	Pos	15	0,0,1,1,1,1,0,0,0,0		11-22-19	Neg
8-19-20	Neg c̄ 3,4 cc	Neg	1			10-20-[illegible]	[illegible]

5 Typical "neurorecurrence" 9 weeks after 6 arsphenamine injections. Developed while on inunctions. Patient entered with chancre, no secondaries.

CEREBRO-SPINAL FLUID 256111

Date	Wass. Comp. Fix.	N.	Cells	Gold Sol.	Drain	Comp. Fixation Date	
1-23-19	Neg c̄ 3/4 cc	—	1			1/17/19	+++
4-26-19	+++ c̄ 3,4 cc	Pos	496	5,5,5,5,5,4,3,2,1,0		2-14-19	Neg
5-19-19	+++ c̄ 3,4 cc pos	Pos	23	4562332011		4-23-19	Neg
5-26-19	Neg c̄ 3,4 cc	Pos	8			5-21-19	+++
6-2-19	+++ c̄ 3,4 cc	Pos	23				

Fluid normal with chancre (after 1 arsphenamine inject.)

Mercury rubs could not prevent this neuro recurrence.

FIG. 7.—VARIOUS TYPES OF NEUROSYPHILITIC REACTION IN PATIENTS WITH EARLY SYPHILIS (PRIMARY AND SECONDARY). The columns to the left of the heavy vertical line are the spinal fluid findings; those to the right are the blood Wassermann reactions. The slight rises in cell count are important indexes of the later and more serious types of cerebrospinal involvement which may occur if treatment is discontinued, or rest periods allowed without examination of the spinal fluid.

slight rises in cell count may have a serious prognostic importance if treatment is reduced in intensity or suspended while they persist. Ordinary treatment may not be sufficiently intensive to prevent the development of a serious grade of involvement in a predisposed person or one who presumably has been infected with a neurotropic strain of spirochete. Early examination of the spinal fluid in primary and secondary syphilis, therefore, serves to forecast the need for more intensive measures and to sort out those patients who may develop grave complications and require intraspinal treatment (Fig. 7). The Wassermann test on the spinal fluid is not sufficient, and unskilled performance of the puncture or delay in counting the cells may obscure a pleocytosis, if present. The first zone gold sol, while important, is not in these cases proof of a paretic outcome. Moore, in a survey of asymptomatic neurosyphilis, believes that, if only one spinal fluid examination can be made, the optimal time is at the end of the first year. Ravaut has contended that the optimal time is before the end of the fourth year. A single examination of the spinal fluid does not, it seems to me, comport at all with the safety and availability of the procedure in expert hands, or the value of the information which it can give.

It cannot be too vigorously emphasized that the information given by the spinal fluid examination in cases of early syphilis cannot be obtained by any other means. These patients are neurologically asymptomatic, and it is precisely when they are so that the complication should be detected and effectively treated before degenerative signs appear. To proceed indefinitely with the treatment of early syphilis, or to introduce rest and observation periods, or discuss cure, without examination of the spinal fluid, may now be regarded as essentially equivalent to malpractice.

THE MANAGEMENT OF SPECIAL TYPES OF SYPHILIS

At one time or another in the foregoing presentation, practically all the principles of the treatment of the various types of syphilis have been discussed and they are here merely sorted out for summary.

Prophylactic Treatment

Medical prophylaxis of syphilis may be properly regarded as part of the early treatment of the disease. While the advent of the arsphenamins has resulted in a systemic prophylaxis, local prophylaxis, which originated with Metchnikoff, Roux and Maisonneuve, has been widely applied among armies and navies and sustained a very thorough try-out among the American Expeditionary forces during the War. The excellent summaries of Riggs, Colonel Ashburn and Walker indicate that the method, provided it is promptly and intelligently applied, has a marked effect on venereal morbidity. Ashburn has expressed the opinion that 1 infection resulted from each 30 exposures without prophylaxis, as compared with 1 infection from each 90 exposures with prophylaxis. Walker mentions a report of 10,000 cases in which prophylaxis taken within the first hour resulted in only 0.08 per cent failures. Rigorous prophylaxis among negro troops at St. Nazaire reduced the annual rate of syphilitic infections from 625 to 35 for each thousand each year.

The essentials of the local prophylaxis of syphilis are:

1. Thorough washing of the genitalia with soap and water.
2. The vigorous inunction into all exposed parts of a 33 per cent calomel ointment made up in a base of equal parts of lanolin and lard. The proportion of calomel, as shown by Metchnikoff's experiments, must be neither more nor less than 33 per cent. Prompt application is absolutely essential to successful prophylaxis, and the percentage of infection rises rapidly when prophylaxis is applied after the first hour. Moore has pointed out that washing with soap and water, while a necessary preliminary to all forms of prophylaxis, is particularly important in preventing chancroid. Immediate urination after exposure and the use of 10 per cent argyrol or 2 per cent protargol solution injected into the urethra forms the prophylaxis for gonorrhea. Efforts have been made to combine prophylaxis for all venereal infections in one preparation, and for this purpose 1 per cent phenol and 3 per cent camphor may be added to the calomel ointment. Bachman recommends tricresol and Colonel Harrison recommends 2 per cent thymol.

Station prophylaxis is definitely recognized as more effective than packet prophylaxis. The physician who undertakes to apply prophylaxis in private practice should, if possible, personally supervise its use by the patient and insist on the thorough and vigorous carrying out of the soap and water cleansing and the rubbing-in of the calomel ointment. The rubbing-in should occupy at least ten minutes, and the excess should remain on the genitalia for at least twelve hours. Neisser's Javanese work, according to Walker, led him to prefer a soluble mercurial, such as mercury bichlorid, but calomel prophylaxis is the accepted technic at the present day. While calomel prophylaxis may be used on suspected abrasions, it must be recalled that infected deep needle punctures are not reached by the rubbing of calomel ointment on the surface of the skin.

The use of arsphenamin as a prophylactic against syphilis was suggested and tried experimentally by Magian and has since been studied by several authors, including Michel and Goodman, Nicolau and others. It appears to be approaching a demonstrated effectiveness, when employed sufficiently early. The administration of three successive doses of 0.6

to 0.9 gm. neo-arsphenamin on three successive days may be regarded as probably efficient prophylaxis. The patient should be cautioned to remain under observation, and the Wassermann reaction should be taken once a month thereafter for at least one year, and observation encouraged for several subsequent years.

Treatment of Early Syphilis

Do not undertake the prophylactic treatment of syphilis with arsphenamin later than three or four days after a known exposure. Do everything possible to secure an early diagnosis in a suspected active case. A darkfield examination should be made on any genital lesion or on any moist lesion elsewhere. If the darkfield is negative, a Wassermann test should be made weekly for several weeks, and monthly thereafter for at least four months. The patient should be warned that his condition is under suspicion, and should govern himself accordingly.

Estimate the contra-indications to intensive treatment on the first visit by a physical examination and an examination of the urine.

The moment convincing evidence of syphilis presents itself (positive darkfield or repeatedly positive Wassermann reaction) begin treatment. Use the ready-prepared solution of arsphenamin, if facilities are lacking for preparing it, in preference to neo-arsphenamin. The first dose should not exceed 0.4 gm. in a robust adult, and the next two doses should be given on alternate days, using 0.4 to 0.6 gm. with each injection, depending on the weight of the patient. The course may then continue to eight injections with doses of 0.4 gm. arsphenamin at weekly intervals, with careful watching for complications. During the last four weeks of this course, the patient should begin the use of mercury either by inunction or intramuscularly, and this mercurialization should continue throughout the six weeks following the end of the first course and on into the first two or three weeks of the second course. The second, third and fourth courses should consist of weekly injections of arsphenamin, 0.4 to 0.5 gm. with six-week intervals between courses. The overlapping of mercurial treatment with arsphenamin from this point on should be so carried out that there will be no time in the first year when the patient is not getting one or the other, and about one-half of the time in which he is getting both together. Rest periods and treatment by mouth are two things which are absolutely excluded, in my opinion, from a sound régime for early syphilis. This so-called continuous treatment has the support of syphilographers such as Irvine of the University of Minnesota, and Keidel and Moore of Johns Hopkins University.

Never proceed with the treatment of early syphilis without ascertaining comparatively early the state of the nervous system as evidenced by the spinal fluid and not by the neurologic examination. The spinal fluid should, if possible, be tested after the second arsphenamin injection (not with the first). If not, it should always be tested before the patient goes on the six weeks' interim mercurialization. It is precisely toward the end of the period of mercurialization or immediately after it that the risk of neurorelapse is greatest, even in a combined system. Slight rises in cell count in the spinal fluid may forewarn of just such an occurrence (see Fig. 7) and should be made the signal for adding large doses of iodid, pushing the arsphenamin and substituting a soluble mercurial salt for an insoluble salt or inunctions, provided the latter had been used up to this time. If any abnormality appears in the fluid at the time of the first examination, the test should be repeated, if possible, at the beginning of each subsequent course and, if abnormal, at least at the end of the course. It is a matter of a good deal of question whether the average practicing physician should attempt the treatment of that proportion of patients, approximating 6 to 10 per cent, who, with a strongly positive Wassermann reaction and high cell count on the spinal fluid are likely to run a resistant course. Such cases call for so much complicated manipulation and management that it is fairer to the patient to place him in the hands of a specialist. On the other hand, in cases that show only a moderate rise in cell count, it is permissible for the physician to endeavor to increase the intensity of his treatment sufficiently for control. A patient with involvement of the nervous system should not, under any circumstances, be placed on a period of complete rest from treatment until spinal fluid findings are reduced to normal and have remained so under treatment for at least six months.

The negative blood Wassermann reaction should be practically dismissed by the average physician as a guide to the discontinuance of treatment in early syphilis. The reversal from positive to negative reaction is to be expected by any efficient treatment technic by the fifth or sixth week. If the Wassermann reaction has persisted strongly positive beyond this time, I have usually been able to criticize the intensity of the methods or the effectiveness of the drugs employed, or to find evidence of involvement of the nervous system. It must, however, be remembered that a highly cholesterinized antigen may yield an occasional faintly positive Wassermann reaction almost indefinitely in patients who have none the less been efficiently treated. The provocative procedure in the form of seven successive Wassermann tests after a 0.3 gm. injection of arsphenamin, may bring out a positive reaction even after several negatives, or a faint or doubtful positive. This is a valuable aid in recognizing pseudocures, but *is not proof of the cure of syphilis in itself.* Just how far it is wise to go in regard to this positive Wassermann reaction as an evidence of active syphilis cannot be conclusively stated, and consultant advice should be sought.

The maximum of safety for the patient with early syphilis is attained by giving treatment in every case to a maximal standard, quite irrespective of clinical or serologic signs of cure. Once the Wassermann-bound treatment tradition in early syphilis can be done away with and vigorous methods pushed to a finish in every case, we shall reach the irreducible minimum of relapse and special involvement, and of complications which are unavoidable with the limitations of our present knowledge of the disease. This, in Moore's opinion and my own, should average about 5 per cent of unavoidable neurosyphilis and perhaps 5 per cent for other types of late complications.

The mercurialization of an early case must be managed with the possibility of recurrence in view. In my experience, insoluble salts have a relatively low efficiency and should be used rather to produce a storage depot of mercury for absorption than to supply the mercury for rapid development of immunity. This latter function is better performed by inunctions or by injecting daily a soluble salt. Where inunctions can be freely employed, courses of eighty should be given, six each week, followed by a rest period of one month, this rest period to be adjusted so as to come during an arsphenamin course. I regard 300 30-gr. mercury inunctions as a minimal requirement in an early case, given in courses of 40 after the first year, with rest intervals of one month. Ten injections of 2 gr. mercury salicylate each may be regarded, in a sense, as equivalent to a course of 40 4-gm. (30-gr.) inunctions. The amount of stored mercury accumulated by a patient who attempts to substitute mercury salicylate injections for a soluble salt or rubs throughout his entire three years of treatment is so large as to constitute a positive danger and has a therapeutic efficiency so low that such a patient may expect relapse rather than cure, if his arsphenamin has not radically cured him. Throughout the second year of the period which should elapse after treatment before the patient is considered out of probation, the physician should keep in the closest possible touch with every aspect of the case. The mucous membranes, the genitalia, scrotum, anus, palms and soles should be inspected, and the patient told what to look for. Inquiry into headaches, disturbances of vision, vertigo, and impairment of hearing are important. The patient should be impressed and reimpressed with the details of his hygiene and his marital or sexual life carefully controlled.

After completion of the course of treatment outlined, the patient who has run an absolutely asymptomatic course may be expected to return for observation once every six months. If the examination of the spinal fluid has been negative, it is unlikely that there will be any recurrence in the nervous system. On the other hand, this possibility must not be lost sight of, and it is desirable to have the spinal fluid examined twice during the ensuing two years.

In the existing state of our knowledge of primary syphilis, I am advising in early cases that patients never entirely abandon observation. Once in two years, at least, merely as a matter of precaution, they should have a thorough check-up both clinically and serologically.

An alternate type of treatment to that proposed was devised by Pollitzer and, while my experience with it is limited, it has received favorable mention. If there is any field of syphilis in which it could be applied to advantage, it is the very early stages of the disease. This treatment depends on the spirillicidal action of arsphenamin. Pollitzer himself regards the resistance-building action of the mercury, which is employed in the intervals, as of secondary importance. Three maximal injections of arsphenamin on a dosage basis of 0.1 gm. for each 25 pounds of body weight are given on three successive days. This is followed by mercury salicylate injections intramuscularly for eight weeks, 2 to 2.5 gr. to the dose. After a complete rest interval of two months, the three injections of arsphenamin are repeated. In Ormsby's modification of the procedure, three maximal doses are given, on alternate days. I have employed four injections on alternate days and given each succeeding arsphenamin course immediately on the heels of the mercury salicylate because of my distrust of the rest interval. If the serologic and symptomatic response is satisfactory, three or four such courses bring the patient to his period of observation. Spinal fluid and clinical symptomatology must be closely watched, as in all early cases.

Relapsing Types in Early Syphilis.—The physician must be cautioned over and over that no system of treatment ever devised has 100 per cent efficiency. Relapses are inevitable in a certain proportion, and only continued insistence on observation and rechecking will ever enable one to know the actual status of his patient, once the period of visible lesions is past. Recurrence in inadequately treated syphilis may assume preponderantly four forms. The first is the simple blood Wassermann relapse, in which no detectable lesions appear but the Wassermann reaction becomes positive after a period of definite negativity and remains so, or fluctuates. In such cases, it is always somewhat of a question whether the Wassermann reaction has ever really become negative in the first place. The second type includes the complete reappearance of the primary lesion (monorecidive) or any or all phases of the secondary manifestations, from a second secondary eruption, to the mucous, palmar and anogenital recurrences which are so often overlooked. See discussion of Case 2 on page 523. The third type is the symptomatic neurorecurrence involving by preference the second, seventh and eighth nerves. The fourth type includes premature tertiarism, either in the form of destructive gummatous cutaneous lesions, or gummatous involvement of the bones, the viscera, or the nervous system (brain gumma).

Case 3.—This patient, a young man aged twenty-three years, developed a penile lesion in February, 1920. He visited a physician, who diagnosed the lesion as a chancre by inspection and took no Wassermann test. Four weeks later, a secondary eruption appeared. The physician then gave him two arsphenamine injections intramuscularly and twelve intramuscular injections of gray oil, whereupon all secondary lesions disappeared. Treatment was then discontinued, the physician assuring the patient that he was well. Four months later the secondary eruption reappeared. The genital lesion likewise reappeared. Acting on the physician's assurances, the patient had then been married two months. Besides the reappearance of the primary and secondary lesions, he also developed iritis.

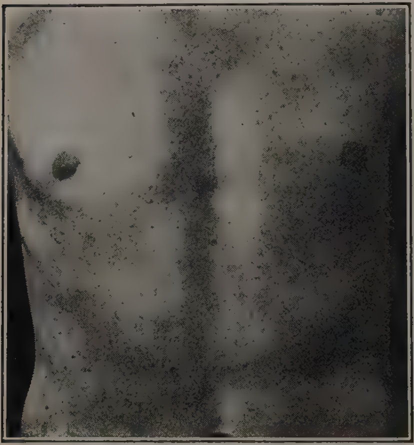


FIG. 8 (CASE 3).—A RECURRENT SECONDARY ERUPTION IN A PATIENT. The primary lesion and first secondary eruption were aborted but the patient was not cured because the treatment was insufficient. The history of this case is given on page 534. Note how inconspicuous the cutaneous recurrence may be. The gravest part of this recurrence was in the optic nerve.

The patient entered the Clinic in October, 1920, nearly blind with neuroretinitis. The Wassermann reaction on the blood was strongly positive. The spinal fluid Wassermann reaction was negative, globulin negative, 33 small lymphocytes. There was nothing to suggest a reinfection. The patient had apparently undergone a complete relapse, with neurorecurrence, as a result of inefficient treatment.

Reappearance of the primary lesion may occur after even the first full course of treatment by a fair technic, provided a premature rest interval is introduced. It is, however, more often the result of low therapeutic efficiency of the drugs used (neo-arsphenamin for example), too small doses, or neglect of mercury. This is the so-called monorecidive, and Spirochætae pallidae are demonstrable in the recurrent lesion which distinguishes it from the gummatous recurrence or pseudochancre redux. Such lesions may be confused with papular recurrences of a secondary eruption (Fig. 8, Case 3) or be taken for reinfections, a fact all too easily overlooked in reports of cures confirmed by this means. The delayed appearance of a secondary eruption of moist secondary lesions as long as two or three years after the apparent aborting of the primary lesions is particularly to be watched for in patients who have presented themselves for treatment very early. Even those who were Wassermann negative on the blood at the time treatment was begun are not insured against this form of recurrence. For this reason it is well to insist on stripping all patients for examination on their return visits and to look particularly for follicular recurrences, palmar lesions and alopecia, as well as moist lesions around the genitalia and mucous membranes (Figs. 9, 10, Case 44, and Fig. 11, Case 5).

The third type of relapse, the so-called neurorecurrence, may occur with both the blood and the spinal fluid negative. It is more common, however, to find both positive, indicating that the relapse is really only a symptomatic expression of what was, up to this point, an ordinary asymptomatic early neurosyphilis, which by neglect has been allowed to go on to actual damage. The onset of symptoms may come from a clear sky in a patient apparently well in all other respects, and consist of rapidly failing vision (Case 6, page 538) unilateral or bilateral, and often permanent facial palsy, sudden and complete deafness of one or both ears, or the labyrinthine syndrome of vomiting, tinnitus and vertigo. It has been much argued that these occurrences are evidences of the trophic power of arsphenamin and its tendency to favor involvement of the nervous system. Personally I regard them, in the majority of cases, as evidence of errors in treatment technic, or of the ignorance or incompetence of the physician, rather than the fault of the arsphenamin as such. They are by no means rare with mercury alone, and can be reduced to an almost negligible element among complications by a rationalized intensive system of treatment.

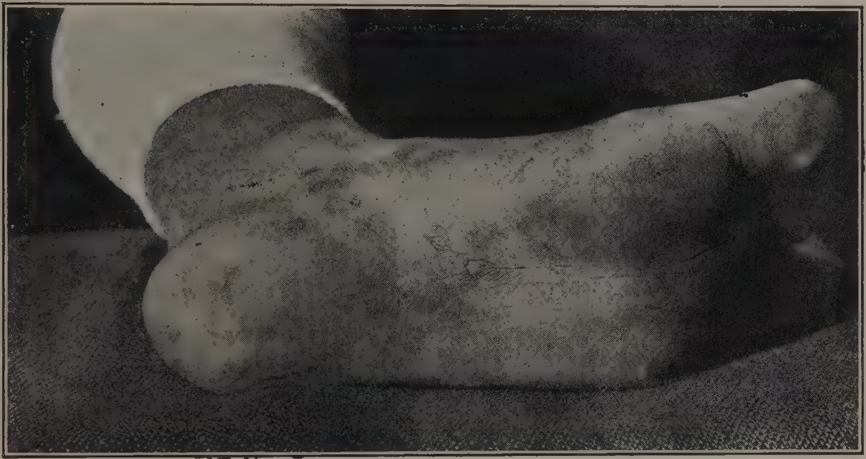


Fig. 9 (Case 4).—Papular Recurrences on the Sole of the Foot in the Same Patient Shown in Figure 10. The patient also had a ringworm.

The headache of a patient with early syphilis under observation should not be lightly dismissed. It may be evidence of an early meningeal lesion, or of ostealgia or osteitis for which a definite point of tenderness can be found on the skull. While it may at times be due to syphilophobia and anxiety, it is surprising how many physicians will permit mere reassurance in such cases to take the place of definite information obtainable by careful examination of the patient. Positive spinal fluids often reveal the cause. In such cases, the blood Wassermann reaction may be negative on a single test, and only become positive in a provocative series.

Case 4.—This case represents a type of infection with which every physician who deals with syphilis under modern conditions should become familiar. The chancre had occurred three years before the patient's first examination at the Clinic, in January, 1922. The diagnosis at that time was made by inspection, apparently without Wassermann or darkfield examinations, and the patient received ten arsphenamine injections at five-day intervals, with complete involution of the lesion.

Four months after this treatment the first relapse occurred, in the form of secondary scrotal recurrences. The Wassermann reaction was positive. Ten arsphenamine injections, five intramuscular mercurial injections, and twenty inunctions were given. The lesions disappeared.

Ten months after the primary lesion, the second relapse occurred, and the patient was given five injections of neo-arsphenamin at five-day intervals.

Three months before coming to the Clinic the third relapse began, again involving the scrotum and accompanied by mucous patches on the tonsils and an eruption on the soles of the feet. The patient asserts that at this time he visited a physician who told him that *it was impossible for him to have syphilis after the amount of treatment he had received, and that he should forget it.* He came to the Clinic at our request, following the discovery of a syphilitic cornee of the palms and a basilar meningitis with syphilitic neurasthenia in his wife.

Examination of the patient in the Clinic revealed findings as follows:

1. Mucous patches at the upper poles of both tonsils. The darkfield examination was positive for Spirocheta pallida.
2. Annular scrotal recurrence (lower lesion, Fig. 10) and moist scrotal papule (upper lesion, Fig. 10).
3. Firm shotty papules with slight scaling forming a distinct arc, on the soles of both feet and the insteps (Fig. 9). One or two suggestions of deep vesicles on the sole of the foot. Marked hyperhidrosis.
4. Blood Wassermann reaction strongly positive; spinal fluid, 6 lymphocytes, otherwise negative.

[*This patient had both a syphilid and a trichophytic eruption of the sole of the foot.* The *Trichophyton* was subsequently found in the top of a dried vesicle.]

A physician need feel no hesitation in diagnosing syphilitic recurrences merely because the patient has had prolonged and energetic treatment. Some patients relapse in spite of every therapeutic effort.

The fourth type of recurrence, premature tertiarism, while it may occur in any type of case or treatment, is often an expression of the allergy induced by a method of treatment which does not use the resistance-building elements such as mercury and prolonged moderate-dosage arsphenamin. An outburst of rupia or an enormous ulcerative late syphilid a few months after the primary lesion, with a sharp constitutional decline, is the commonest form (Fig. 12, Case 7). Brain gumma, which may perhaps better be regarded as a form of neurorecurrence, may occur. As a rule, however, those patients who develop the marked cutaneous and osseous reactions seem to be protected from serious nerve involvement and, when vigorously treated, make a good and apparently permanent recovery.

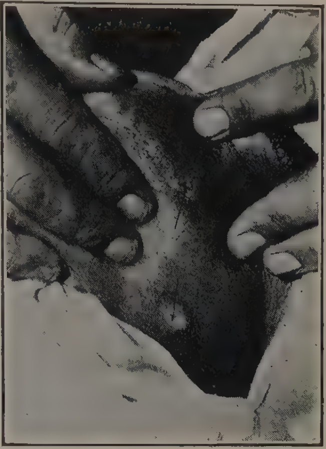


Fig. 10 (Case 4).—Recurrent Mucous Patch of the Scrotum. Spirochæta pallida present in a patient who had been assured by his physician that he was cured, after twenty-five arsphenamine (neo-arsphenamin?) injections, five intramuscular injections, and twenty inunctions. The patient was seen in the Clinic in his fourth relapse.

The first step in the management of a recurrence is a critical review of all previous treatment. In this the physician should not spare criticism of himself and his patient. If his procedure has conformed to the ideal, he may accept the relapse as inevitable, but not otherwise. Particularly it is essential to stress the time intervals, to inquire into the proportion of rapidly to slowly absorbed mercury which the patient has received, and the care employed in maintaining the patient's defense as well as destroying the spirochetes. It is relatively seldom that the physician does not find some point at which he may seriously criticize his management of a case which shows a marked tendency to relapse. In particular, I have been led to distrust neo-arsphenamin, in my observation of these cases, and I feel disposed to insist that the subsequent treatment of any recurrence must be at the hands of an expert who can employ arsphenamin with full efficiency.

Case 5.—The primary infection in this case occurred in November, 1919, although the patient gave a history of a supposedly syphilitic infection sixteen years before. He has run the typically relapsing course of the irresponsible patient who receives a little treatment here and there, without systematic, intensive management. The authenticity of the alleged first infection may be doubted.

At the time of the patient's first appearance in the Clinic he had a tremendous outburst of mucous lesions, papular secondary lesions, and apparently a precocious gumma of the nasal septum as a relapse following six arsphenamine injections and mercury by mouth. He responded promptly to another six arsphenamine injections and then disappeared from observation. Nine months later, he took three more injections, and again disappeared. Six months after his second disappearance, he returned with the scrotal recurrences here illustrated, and with mucous lesions in the mouth. During his lapses in treatment he had evidently had repeated herpetic and moist lesions and had developed a syphilitic laryngitis with an ulcer of the false cords.

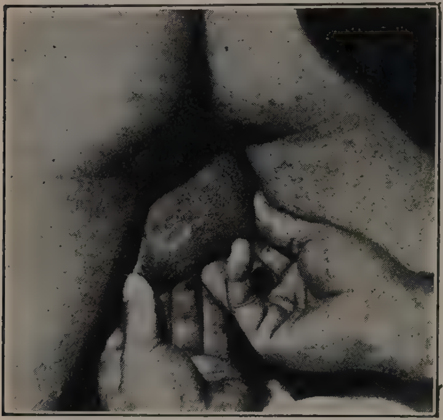


FIG. 11 (CASE 5).—TYPICAL ANNULAR SCROTAL RECURRENCES. The average physician does not appreciate the value of examining the posterior surface of the scrotum for signs of relapse in early and latent syphilis.

This is the typical course of an infectious relapsing type of case. It is a particularly alarming and serious defect in the inadequate treatment methods so often applied to early syphilis, that the symptomatic response is so striking that the patient as well as the physician is entirely thrown off guard, and the patient sometimes sustains an almost indefinite prolongation of his infectious recurrent period, to the grave danger of the public.

Only systematic examination will disclose lesions of this sort. They are practically symptomless.

Case 6.—A laborer, aged 32 years, registered at the Clinic, giving a history of penile lesions and secondary eruption 6 months before. He had received five intravenous arsphenamine injections, and potassium iodid by mouth, but no mercury. One month after the last arsphenamine injection, his vision had begun to fail and a violent, rapidly progressing neuroretinitis was recognized.

The physical findings were negative. The Wassermann reaction on the blood was negative. The spinal fluid was normal. An extraordinarily rapid improvement, with almost complete recovery of vision, occurred under the intensive use of mercury succinimid and sodium iodid intravenously, followed by arsphenamin. Four arsphenamine courses were given as for an early infection, with 200 30-gr. inunctions and 325 gm. of sodium iodid intravenously. Six weeks from the date of his last arsphenamine treatment, he developed multiple penile lesions, 2 weeks after a drunken spree. The old penile scar showed some induration but no erosion or other sign of activity. Spirochæta pallida were found 8 days later in a small indurated lesion at some distance from the chancre. The

Wassermann reaction on the blood was strongly positive (lesions several weeks old). Twenty days after his return, maculopapular secondaries appeared. On this occasion, there was no involvement of the optic nerve. The spinal fluid was normal. His wife developed a chancre of the cervix.

The eye complication of the first infection was typical of a neurorecurrence following inadequate treatment. Even the negative spinal fluid is not unusual. It is conceivable that the second infection was a relapse rather than a reinfection, but the evidence in general is more suggestive of reinfection. The second infection has run a very different course from the first. A superinfection is, of course, not inconceivable. If this is a reinfection, it indicates that advanced involvement of a part of the nervous system (optic nerve) may occur and yet the infection may be susceptible of radical cure.

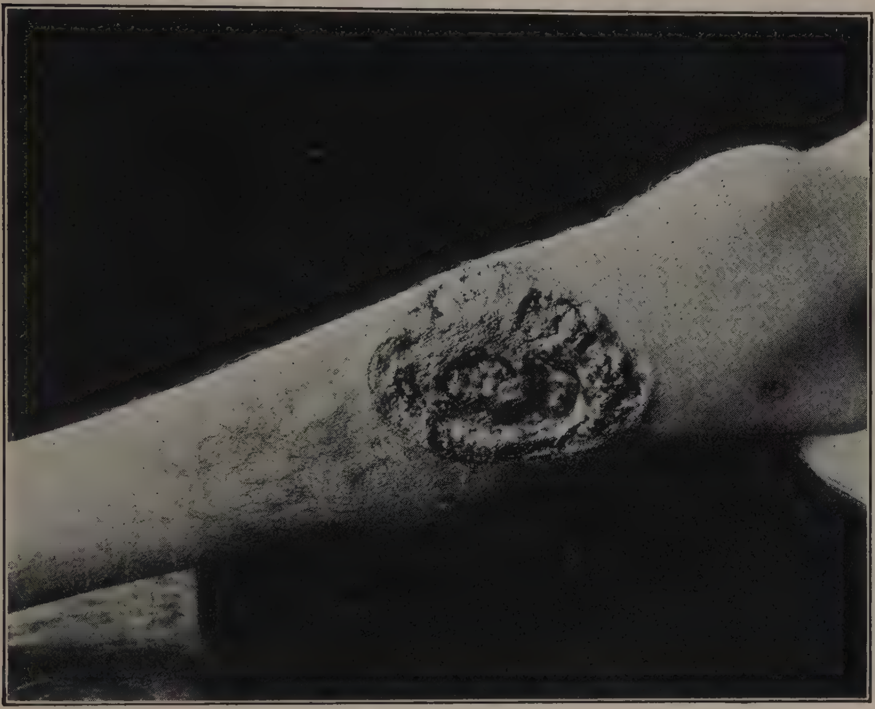


Fig. 12 (Case 7).—Precocious Tertiarism.

Case 7.—This patient had had syphilis for nine months, and had developed a lesion more appropriate to the ninth year of an ordinary syphilitic infection. While such a course is possible in any type of case, in this instance the sequence of events was that more often seen in patients who, because of the exclusive use of arsphenamin, do not develop immunity to the disease. This boy received one injection of arsphenamin when his primary lesion was one week old. The chancre cleared up and nothing further was done.

Three months later his throat swelled and became so sore that he could not eat. A diagnosis of tonsillitis was made, but when he became steadily worse during five weeks of local treatment he was given three injections of neo-arsphenamin, and promptly recovered. This was evidently his secondary angina.

Four months passed without incident, when suddenly red spots and small lumps appeared on arms, legs and scalp. These developed rapidly into crusted ulcers, and the lesion over the tibia became the typical enormous gummatous ulcer shown in the photograph. The scars of the smaller lesions were those of rupia, and the conjunction of the two types of lesions shows their similarity. The patient was then given mercury for the first time (inunctions), and sodium cacodylate, which is worthless in the treatment of syphilis.

This patient had had two successive postarsphenamine relapses, with a rapid advancement of the immunologic aspects of the disease to the hyperallergic condition of late syphilis. As a result, he developed a rupia as a sort of delayed secondary eruption, and, with it, a huge gummatous ulcer. His condition had become so serious and resistant that comparatively little response could be secured from ordinary therapeutic measures.

The Wassermann reaction on the blood was negative repeatedly. Spirochætae pallidae are not demonstrable by darkfield in lesions of this type. Premature tertiarism less frequently exhibits infectious mucous recurrences than the mucous relapsing type.

To treat a recent syphilitic infection with a few scattered doses of arsphenamin or neo-arsphenamin on a symptomatic basis, without developing immunity by the use of mercury, is to invite premature tertiarism and precocious malignant syphilis.

There is no system of treatment which can guarantee certain relapsing types of cases against subsequent relapses (Fig. 13, Case 8). The Pollitzer system has been commended for its ability to reverse the seemingly irreducible or relapsing blood Wassermann reaction. If something can be definitely criticized concerning the previous treatment in a relapsing case, it may be well to place the patient outright on a system of early treatment again, disregarding entirely whatever has gone before. The treatment of neurorecurrences and resistant neurosyphilis by ordinary methods may be satisfactory, but if previous treatment has been even reasonably vigorous I believe it is much better to add intraspinal treatment, if the reaction of the fluid is positive, and large doses of iodid intravenously with mercury bichlorid, succinimid or biniodid intramuscularly, in preference to merely playing with moderate doses of arsphenamin and the insoluble mercurial salts which proved inadequate in the first place.

The possibility of completely changing the line of attack in these cases by the use of silver arsphenamin or sulpharsphenamin and of bismuth intramuscularly should be considered.

When the question of relapse versus reinfection confronts the physician, it is better to start all over again, treating the patient as though he had never been previously infected, than to favor still another and perhaps more serious recurrence by inefficient treatment of the presenting lesion.

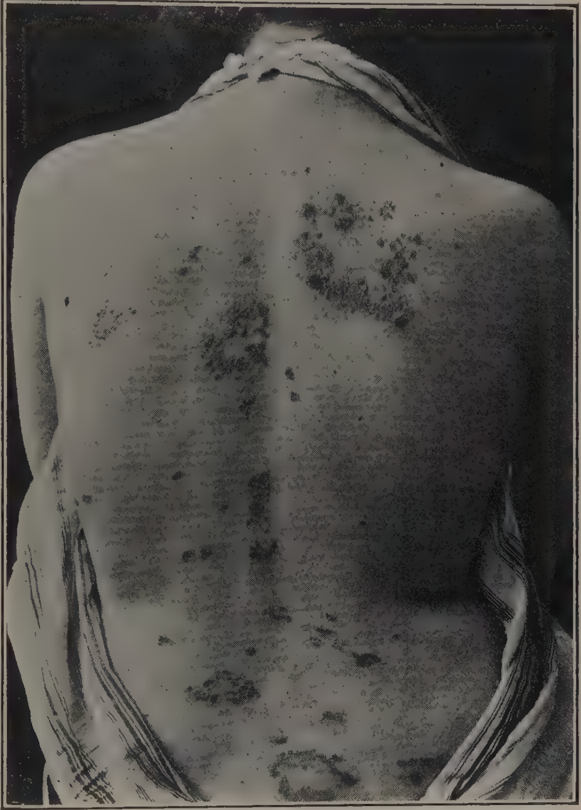


Fig. 13 (Case 8).—A Corymbose Papular Recurrence, after Twenty-four Arsphenamine (606) Injections and 257 30-gr. Inunctions.

Case 8 (See Fig. 13.)—All the 24 arsphenamine injections and 137 of the inunctions were given in the first ten months of treatment. The patient had had an extragenital (tonsillar) primary lesion, and a secondary eruption was present when she was first seen at the Clinic. She followed treatment assiduously, in accordance with a rigorous standard, yet the relapse appeared one year after the last arsphenamine injection, while she was in the midst of a course of inunctions. The Wassermann reaction on the blood, which had been negative since the beginning of the second course, became positive. There was no evidence of reinfection, although this possibility must be considered.

Patients with recurrences are by all odds the most dangerous from the standpoint of carriers and as a menace to public health. They require the closest clinical watching, and permission to marry or to have sexual relations should be granted only with the greatest circumspection, or be withheld indefinitely. Cases of the type here discussed re-emphasize the importance of life-long observation rather than rash statements about cure in syphilis.

Management of Latent Syphilis

The complete physical and serological appraisal of the case, including several blood Wassermann tests, the spinal fluid examination, a cardiovascular examination, careful study of the pupils, deep reflexes and sensory responses, palpation and even Roentgen-ray examination for bone lesions, is desirable. The fundus of the eye must be examined. In other words, the physician must be sure that his case is *latent.* If it is latent (positive Wassermann reaction only), the age element and the duration of the infection from the standpoint of possible transmissibility and future complications must be carefully weighed. It is better to be prophylactically minded and to err on the side of protecting the patient and the public when there is a possibility of transmitting the disease, or of later complications, than to be too afraid of disturbing the resistance-defense mechanism. It must be said, however, that once treatment is begun it should be continued, through three full courses of six arsphenamine injections each. Inasmuch as the purpose of such a course is immunity-building, even more than the extermination of all spirochetes, the interim between arsphenamine courses should be four months divided into rest periods of a month before and a month after each course of forty inunctions, the total being approximately 300 30-gr. rubs. Depending on the patient's circumstances, it may be desirable to provide a storage depot by one or perhaps two courses of mercury salicylate, especially toward the last. The patient should be impressed with the fact that once every year or two he should return for a general investigation of his condition. This observation should not be limited to a blood Wassermann test, but should repeat essentially the complete physical appraisal called for at the outset.

Management of Late Active, but Benign Syphilis

Certain types of syphilis, even though active, are recognizably benign. For example, a positive blood Wassermann reaction and a small, only mildly destructive bone lesion in a patient over fifty years of age do not call for the utmost resources of modern syphilotherapy. As a preliminary to deciding on the benign character of the manifestation, a physical appraisal of the patient, as I have mentioned, is, of course, necessary. If a physical appraisal fails to reveal anything beyond the benign presenting symptom, the treatment decided on may range from a course of from six or eight small injections (3 to 6 dg. of neo-arsphenamin), followed by one or two courses of inunctions with iodid, to mercury and iodid by mouth without arsphenamin. On the other hand, if the patient is younger, or presents a lesion which while essentially benign in character is none the less resistant and disfiguring (as in gumma of the nasal septum or hard palate), a long and vigorous course may be necessary. As a rule, however, it seems better to work for resistance in these cases rather than for mere spirillicidal effect. Especially in obstinate bone lesions in the nose, course after course of inunctions with iodid in 20 to 50-gr. doses three times a day over a period of months may result in ultimate involution even though the Wassermann reaction may remain positive.

The removal of sequestra in osseous lesions may be necessary to ultimate healing. Such a procedure as amputation is rarely necessary if treatment for syphilis is pushed with full effectiveness.

Management of the Syphilitic Mother

The prophylactic value of treatment during pregnancy, and even treatment in preparation for conception, deserves reëmphasis. At the same time, the fact must not be lost sight of that the pregnant woman is already somewhat under the protection of one of the immunity-producing conditions affecting the physiologic course of syphilis. The tendency of a syphilitic infection to become latent during pregnancy and lactation is sufficiently marked to make one almost feel that pregnancy for the syphilitic woman should be in a sense part of her treatment, provided she can be insured a healthy child. The pregnant woman, of course, carries a double load on her excretory mechanism, and Wechselmann was the first to insist that this fact especially demands moderation in dosage. Such moderation, of course, does not necessarily apply to treatment in preparation for conception, which should follow the usual rules.

The earlier in the course of pregnancy that a syphilitic infection is identified, the better. During the nine months of the ordinary pregnancy, it should be possible to give at least one course of eight injections, or preferably two six-injection courses of neo-arsphenamin. The dosage should seldom exceed 6 dg. of neo-arsphenamin, and the interval between injections should be one week. Patients who show a definite tendency to uterine irritability may find it necessary to rest in bed. The mercurialization of the pregnant woman should practically never be carried on in combination with arsphenamin, but should be used as interim treatment preferably in the form of inunctions, provided there is not too much skin irritability. Medication by mouth, at one extreme, and heavy doses of insoluble salts (mercury salicylate) at the other, are in my opinion to be avoided if possible. Arsphenamin is distinctly more important for the child in utero than intensive mercurialization, because of its spirillicidal efficiency. It protects the child from inoculation during the mother's spirochetemia. Mercurialization is more for the protection of the mother against allergic forms of relapse after the birth of the child. The closest possible watch must be kept on the urine, and evidence of pronounced renal irritability indicates a temporary suspension or complete cessation of treatment.

Treatment during pregnancy should not be discontinued after the birth of the child, but should be carried to completion with the employment of normal adult doses. In cases in which the toxemia of pregnancy is complicated by syphilis, acute or latent, the syphilis should not be treated until the toxemia is under control, because of the presumptive additional strain of heavy metal intoxication on the liver and kidneys. Obstetricians, in inducing premature labor in such cases, should exercise the greatest care in protecting themselves from infection. In fact, the identification of syphilis during pregnancy and its proper treatment has enough importance for the obstetrician to justify his insistence on a Wassermann test for his own protection.

The question as to whether a partial positive Wassermann reaction in a pregnant woman is an indication for beginning treatment for syphilis cannot be absolutely answered at the present time, but must depend on the make-up of the case as a whole. A full investigation for evidence of syphilis by repetition of the Wassermann test, and especially when controlled by such technic as that of Kolmer, may establish the actual state of affairs. A single weak positive Wassermann reaction certainly does not constitute a diagnosis of syphilis. On the other hand it is, I believe, distinctly safer, both for mother and child, to accept a repeated strongly positive blood Wassermann reaction during pregnancy as evidence of syphilis, and to give the child the benefit of the doubt by instituting treatment.

Management of Heredosyphilis

The problems of syphilis acquired in childhood are essentially those of the acquired form of the disease at any period in life, and in my experience have been far less difficult than they are reputed to be. Syphilis acquired in utero, on the other hand, has on the one side the possibility of irremediable antenatal damage which comes from the weaving of the infection into the very anlagen of the body structures, and on the other hand the advantage that, if survival does take place, it implies a degree of natural resistance which is a valuable assistance in treatment.

Uterine infections, in an overwhelming proportion of cases, terminate fatally before birth or within the first two years of life. It is this tremendous mortality, aggregating close to 75 per cent, that makes urgent the antepartum detection of syphilis in the mother and antenatal treatment of the child. Broadly speaking, five types of infantile heredosyphilis present themselves for treatment: (1) the child in whom active lesions are recognizable at birth or within the first two or three days of life; (2) the child apparently healthy but born of a syphilitic mother who develops the first outspoken evidence of the disease within the first six weeks to three months after birth; (3) the child who, born of a syphilitic mother, presents a positive Wassermann reaction on the blood from the cord which persists without the development of gross signs; (4) the child who, born of a syphilitic mother, presents a positive Wassermann reaction on the blood for a short time, which then disappears and is not followed by any sequelæ; and (5) the child, born of an apparently healthy mother, who presents one or another of the above signs of syphilitic infection.

The first essential for the management of syphilis in infants is that the mother shall nurse the child for as long as possible, up to one year. This can be done without danger to the mother and the physician should vigorously insist on it. While intensive treatment of the mother has some favorable effect on the nursing infant, this is by no means sufficient to take the place of direct treatment of the child. Arsphenamin is indicated in practically all cases except the fourth type, in which the Wassermann reaction is simply temporarily positive and becomes permanently negative without further signs after from ten days to two weeks.

Few general practitioners are technically equal to giving arsphenamin intravenously to small infants. The prominence of the veins over the skull and the external jugulars may make such treatment possible, however. With the assistance of a competent nurse and a triangular blanket in which the child is wrapped as for an intubation, the youngster can be well controlled. I do not advise or countenance the giving of arsphenamin by the anterior fontanel. Jeans also discourages this method. Fordyce and Rosen have pointed out the feasibility and advantage of neo-arsphenamin and mercury bichlorid intramuscularly in the young infant. Their arsphenamin technic has been described on page 488 and the results which they report certainly seem to justify an increasing popularity wherever intravenous technic is attended with difficulty. Sulpharsphenamin likewise shows promise in this direction. The dosage given intravenously should be regulated by body weight in the same way as in the adult. A seven or eight-pound infant should receive 0.02 gm. neo-arsphenamin for the first injection, 0.05 gm. for the second injection, and 0.1 gm. for the third injection, at intervals of five days. From this point on, the dose should range from 1 to 3 dg. of neo-arsphenamin intravenously according to the weight and general response of the child, for a course ranging from six to ten injections, followed by a four months interim on inunctions. This course should be repeated at least three times. Inunctions are well borne by infants, the rubs being given forty to the course and the dose 1 to 2 gm. of the 50 per cent mercurial ointment rubbed on the back and flanks, and on the binder. Inasmuch as fibrosis is a conspicuous part of the pathologic picture in uterine syphilis, iodid should be begun early, administered with milk by the use of a dropper. If the infant is at the breast and the mother is under treatment, the infant can obtain a considerable dose of potassium iodid through the milk by giving the mother 10 to 50 gr. three times a day. Close attention should be paid to the matter of iodid idiosyncrasy in infants, because fulminating bullous iodism may be the first warning of intolerance.

Arsphenamin and mercury should be alternated in infancy to obtain the full tonic effect of the arsenical. I have seen very little occasion to use mercury by mouth in the management of infantile syphilis. Mercury intramuscularly may be given in the form of the bichlorid or succinimid, 1/24 to 1/12 gr. daily, in cases in which a rapidly destructive process is making headway in spite of ordinary measures.

The general nutrition of the child demands close attention during this period. The principal effort should be to tide the child along with nursing and treatment until it has grown to the point where a certain measure of physical independence and increasing vigor permits the use of more intensive measures if they are required. The spinal fluid examination is quite essential in infantile syphilis and by the time the child reaches one year of age should certainly be performed. The idea that involvement of the nervous system is rare in cases of heredosyphilis is distinctly erroneous.

The infant born without lesions but with a positive Wassermann reaction on the cord blood, if apparently robust, should be watched for a period of several weeks before treatment is instituted. During this time the Wassermann test can be repeated and, if the reaction is persistently and strongly positive after the second week, treatment with neo-arsphenamin and mercury should be begun. Three courses have been my customary minimal requirement irrespective of Wassermann findings in children both with and without active lesions.

Tardive Heredosyphilis.—The identification of heredosyphilis in older children either by the Wassermann reaction or by identification of stigmas should, in practically every case, be the signal for treatment. Therapeutically speaking, these children should all be regarded as having late syphilis and the measures adopted should lean towards the resistance-building side. The child who has a repeatedly positive blood Wassermann reaction, or who exhibits definite stigmas in the absence of the positive Wassermann, should not, in general, be permitted to go untreated. While the tendency to relapse is less marked than in acquired cases, any sudden drop in resistance even after the patient reaches adult life may result in the onset of interstitial keratitis, deafness or osseous gummas. The freedom of children with heredosyphilis from cardiovascular accidents is notable, and is especially striking because of the easy demonstration of the spirochete in the heart muscle at necropsy in most untreated cases. Involvement of the nervous system on the other hand is by no means uncommon and all older children with heredosyphilis, especially if the reaction on the blood is positive, should have a spinal fluid examination early in the course of treatment.

While neurosyphilis in childhood has a distinct clinical tendency toward paresis, early detection of the involvement makes it possible to use intraspinal measures and to reduce materially the incidence of late serious accidents. When proper examination and testing of this matter is neglected, a convulsion or a hemiplegic attack or slowly progressive mental deterioration may be the first warning that the positive blood Wassermann reaction was accompanied by a neurosyphilitic process.

In the treatment of heredosyphilis in older children, eye complications, involvement of the eighth nerve, and osseous lesions constitute three of the most trying problems. It has been our experience that arsphenamin is particularly valuable in dealing with interstitial keratitis. It is an incomparable advance over mercury in the promptness of the relief which it gives, in the possibility of forestalling involvement of the other eye and in preventing serious and permanent damage through vascularization. In severe cases, arsphenamin should be employed instead of neo-arsphenamin. The dose should be about one-fourth to one-third greater than by weight, and mercury should be given simultaneously, preferably in the form of a soluble salt intramuscularly. Moderately large doses of iodid, 20 to 50 gr. three times a day, may be given with the arsphenamin and mercury. A child with active interstitial keratitis should not be in school, should avoid other forms of eye-strain, and should protect the eyes from bright lights and sunlight by tinted glasses. The pupil should be kept dilated to a maximum with atropin. Hot compresses should be employed in cases in which there is much vascularization and opacity of the cornea. Treatment should be carried on entirely irrespective of the symptomatic response of the eye and should be pushed to a minimum of three courses of six to eight injections each and, if possible, to a complete and permanent reversal of the blood Wassermann reaction. It is of additional advantage to secure as a therapeutic control an occasional ophthalmologic examination for evidence of activity. The process may progress in mild, chronic form after the photophobia and inflammatory symptoms have subsided, with considerable unnecessary ultimate damage.

Old cases of interstitial keratitis have, of course, only a limited outlook for improvement. None the less I have found it worth while to offer each patient a trial of treatment. One to three arsphenamin courses, a year of inunctions, and two years of iodid may result in a gradual improvement which makes the effort worth while.

Involvement of the eighth nerve in heredosyphilis, if it can be recognized early and has not been too sudden in onset, may be benefited to some degree by the prolonged and determined use of mercury and iodid. This means inunctions over a period of at least three years, with liberal doses of potassium iodid and two to four courses of arsphenamin.

Resistant bone lesions in heredosyphilis, which are the torment of the syphilographer in some of these cases, are in my experience one of the best types of syphilis on which to demonstrate the superior efficacy of combined instead of alternate administration of arsphenamin and mercury. The influence of trauma is important. Iodids should be pushed and operative interference avoided. Casts, and so forth, are seldom needed.

In addition to attention to general measures and the weight curve, the hemoglobin should be watched in cases which are subjected to prolonged hospitalization. The interference with the child's schooling that results from eye and ear lesions should be met by the coöperation of the social worker and, at the earliest possible time consistent with the child's welfare, special training should be begun. The physician can usually obtain information on this matter from the state schools for the blind and deaf.

The management of the Wassermann-fast case of heredosyphilis, in my experience, is not essentially different from that of the acquired case except for a presumptively better prognosis. Two years of consistent therapeutic effort is the minimum before considering the possibility that the Wassermann reaction will not yield to treatment.

The question of the marriage of heredosyphilitic persons is frequently raised. Tardive types are non-infectious and, while there is a distinct tendency towards sterility, I feel that there is no general contra-indication to marriage provided the patient has been systematically treated and is in good health. While the existence of third generation syphilis will probably have to be admitted, the intervention of modern treatment reduces the possibility almost to the vanishing point and there seems to be no convincing evidence that constitutional inferiorities and degenerations are particularly prone to afflict the children of a well-treated heredosyphilitic parent.

MANAGEMENT OF VISCERAL SYPHILIS

Gastric Syphilis.—Gummatous lesions of the stomach may, of course, raise the differential problem of carcinoma. In all such cases with a coincident positive Wassermann reaction, the impulse may be to treat the patient for syphilis to see whether the gastric lesion will not resolve. The advisability of following such a course depends, in our experience, entirely on the clinical and roentgenologic decision as to the probable operability of the supposed carcinoma. If there is reason to believe that the lesion is operable, or if there is a marked degree of obstruction irrespective of the operability of the lesion, an exploration should precede any elaborate or prolonged treatment for syphilis. The question of malignancy can thus be settled, and obstruction relieved if necessary. If the blood Wassermann reaction is positive, it is better to give one or, if possible, two arsphenamin injections of 3 to 4 dg. each, five to seven days apart, before operation in order to secure a therapeutic lead on the process and to protect the surgeon. Further treatment with arsphenamin may be pushed during convalescence if the lesion is found not to be malignant.

When the gastric lesion is obviously syphilitic, or when if carcinomatous it would undoubtedly be inoperable, treatment for syphilis may be begun at once in the form of arsphenamin in doses proportioned to the weight and condition of the patient. The response of gastric syphilis to arsphenamin is excellent. The debilitated condition of the severer cases makes the simultaneous use of mercury undesirable. Cachectic patients should be put to bed, alkalinized and given neo-arsphenamin at the outset. If the syndrome is syphilitic, the response will usually be one of the most remarkable in the whole field of treatment. The first or second injection usually gives complete relief from pain and, if there is no significant obstruction, the gain in appetite and weight is phenomenal. In fact, failure to make a pronounced therapeutic response within the six weeks of the first course argues a possible error or incompleteness in diagnosis, and the patient should be rechecked for the question of linitis plastica, carcinoma or obstruction.

Pseudogastric syphilis, or gastric symptoms accompanying the hypoacidity of systemic syphilis or involvement of the nervous system, responds to treatment for syphilis in approximately 70 per cent of cases. The treatment in these cases should be directed at the major process in the nervous system and not be merely routine or desultory.

Hepatic Syphilis.—Hepatic syphilis is one of the types which is unfavorably affected by too intensive treatment at the outset. Arsphenamin should not, therefore, be used until after some weeks or months of mercurial and iodid preparation. In cases of localized gumma it is better tolerated and less likely to give rise to anasarca from shrinkage and rapid fibrous change, but it is virtually impossible to predict, under ordinary conditions, what course a given case will pursue. Long rest intervals are helpful in enabling the patient to recover from the seemingly unusually depressant effect of even moderate treatment. Restriction of fluids and catharsis may diminish the necessity for tapping, and the latter measure should not be resorted to sooner or more often than necessary. A Talma-Morison operation may give relief, but a surprisingly large proportion of patients will ultimately develop an effective compensatory circulation. Emphasis should be placed on the obligation to reach an accurate diagnosis if possible, before treatment begins. The possibility of malignancy, lesions of the gall tract, and previous injury to the liver by arsphenamin should be carefully considered even though the Wassermann reaction may be positive. Marked and increasing jaundice in spite of treatment is more suggestive of a malignant process than of syphilis.

Splenic Syphilis.—Syphilis of the spleen, especially if the spleen is large, is resistant to ordinary treatment, but persistence will accomplish much more than is at first anticipated. In those cases in which the patient remains below par, in spite of careful treatment, splenectomy may accomplish great and permanent improvement. The operation should not, however, be regarded as a substitute for treatment for syphilis, of one which the inexperienced surgeon should undertake.

Management of Cardiovascular Syphilis

The prognosis of cardiovascular syphilis, probably because it is recognized comparatively late by signs which represent more or less extensive and irreparable damage, is rather poor. Because of its frequency, its remarkable capacity for remaining in concealment, and its poor outlook when it finally is recognized, I have urged the treatment of the patient with latent syphilis with a positive blood Wassermann reaction, even though for the moment there may be no gross indication that his disease is damaging his vascular system.

The lesson of a slow therapeutic approach to syphilis of the cardiovascular system is usually learned at the expense of several necropsies. While there can be no doubt that certain patients with cardiac disease tolerate arsphenamin well, there is abundant evidence to show that, for the more advanced cases especially, it is dangerous at the outset though better tolerated later, particularly if the patient has signs of coronary sclerosis, marked myocardial insufficiency, or an aneurysm of considerable size. The rapid changes produced in the lesion by arsphenamin lead to further and uncompensated reduction of the circulation of the heart muscle, to fibrosis with further conduction impairment, and to edema followed by thinning and rupture of the wall of the aneurysm. All of these by-effects have been apparent clinically in my own experience. It is possible, under arsphenamin, to cause an aneurysm apparently fixed and stationary to increase in size and present through the chest wall instead of improving. A nearly fatal anginal attack can be brought on by one arsphenamin injection in a patient who has had but little disturbance theretofore.

For these reasons, the treatment of cardiovascular syphilis should begin by long mercurial and iodid preparation, and even this must be of the mildest if the symptoms are at all pronounced. Several weeks or months of treatment, at first by mercury with chalk by mouth followed or combined later with inunctions and rest to reduce strain on the healing parts as much as possible, are, I believe, essential to the management of severe cases. Neo-arsphenamin, after several weeks or months, may be begun in small doses, beginning with 0.05 gm. irrespective of body weight, and increasing 0.05 gm. each week to a maximum of 0.6 gm. for from eight to ten injections. Potassium iodid by mouth is usually well borne and may be carried to 30 or 50 gr. three times a day. I have seen no special advantages from sodium iodid intravenously.

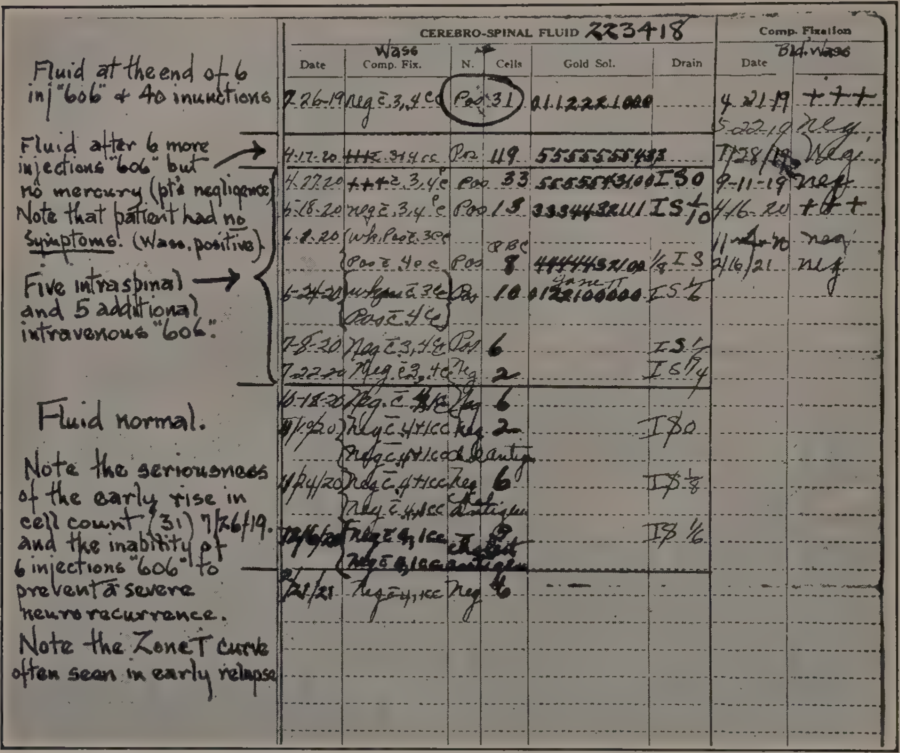
Rest in bed, bromids and reassurance are important elements in the management of all cardiovascular cases. Most patients can be habituated to rest and learn best to reduce their mental tension and hyperactivity in this way. The assistance of occupational treatment is especially important in this group of cases. A few patients cannot endure the restraint of bed, and these must be reëducated without it. Teaching the patient with cardiac disorders to live within his limitations is a large part of the art of medicine in these cases.

For actual breach of compensation the outlook is good the first or second time, and poor thereafter. In the recovery of compensation, I have known treatment for syphilis to be effective when digitalis and rest failed. The digitalizing of a syphilitic cardiopath does not differ essentially from that of any cardiac type. Cardiopaths must not, as a rule, be allowed to gain weight during their confinement in bed. The management of the kidney may call for special care, and intramuscular mercurialization must be avoided unless occasionally in a breach of compensation for a few days rapidly to saturate the patient.

The therapeutic paradox may be seen in cardiovascular syphilis in the development or accentuation of signs of aortitis, or the appearance of fluoroscopically visible pulsation in an aneurysm previously regarded as tumor, after the patient has been under treatment for some weeks. An aneurysm rarely decreases in size, but the relief of the symptoms of mediastinal pressure, such as hoarseness, pain and dyspnea, may be very pronounced.

Management of Syphilis of the Nervous System

It is not within the province of this presentation to discuss the special treatment of syphilis of the nervous system, which is distinctly a matter for special training and facilities. But it is worth while to emphasize that the ideal treatment of neurosyphilis is preventive. Close adherence to a vigorous technic of treating the early case, with proper checks on the behavior of the nervous system in the first year of the infection, and the early institution of intensive measures, will do much to make the treatment of tabes and paresis, now so large a part of the business of specialists, a thing of the past. While in the earlier months of the disease moderate involvement of the nervous system may yield with comparative ease to ordinary methods of treatment, about 25 to 30 per cent of the cases identified at that time are resistant and supply the abundant neurosyphilogic material of later years. These later cases are those which have withstood ordinary methods of treatment early in the disease, rather than those whose nervous systems have become involved *de novo* by extension of the disease after the secondary period or during latency. In the majority of these resistant cases, special measures, such as treatment intraspinally, are likely to be necessary (Fig. 14). While it is proper to begin their treatment with combinations of standard procedures, such as the synchronous use of mercury, arsphenamin and intensive administration of iodid, and perhaps to add spinal drainage, a certain percentage which will not yield to such measures will yield more readily and with less expense and inconvenience to the patient, to expertly applied intraspinal treatment. There always remains, however, the unpredictable residuum which will not respond to any measures.



Fluid at the end of 6 inj "606" + 40 inunctions

Fluid after 6 more injections "606" but no mercury (pt's negligence) Note that patient had no Symptoms. (Wass. positive)

Five intraspinal and 5 additional intravenous "606".

Fluid normal.

Note the seriousness of the early rise in cell count (31) 7/26/19. and the inability of 6 injections "606" to prevent a severe neuro recurrence.

Note the Zone T curve often seen in early relapse

CEREBRO-SPINAL FLUID 223418

Date	Wass Comp. Fix.	N.	Cells	Gold Sol.	Drain	Date	Bld. Wass
7-26-19	Neg c̄ 3,4 cc	Pos	31	0112221000		4-21-19	+++
						5-22-19	Neg.
4-17-20	+++ c̄ 3,4 cc	Pos	119	5555555433		7/28/19	Neg.
4-27-20	+++ c̄ 3,4 cc	Pos	33	5555543100	I S 0	9-11-19	Neg.
5-18-20	Neg c̄ 3,4 cc	Pos	13	3334432111	I S 4/10	4-16-20	+++
6-1-20	wk. Pos c̄ 3 cc		RBC			11-4-20	neg
	Pos c̄ 4 cc	Pos	8	4444432100	1/4 I S	2/16/21	neg
6-24-20	wk. pos c̄ 3 cc Pos c̄ 4 cc	Pos	10	Zone T 0122100000	I S 1/6		
7-8-20	Neg c̄ 3,4 cc	Pos	6		I S 1/6		
7-22-20	Neg c̄ 3,4 cc	Neg	2		I S 1/4		
8-18-20	Neg c̄ 4 cc	Neg	6				
9/1/20	Neg c̄ 4+1 cc Neg c̄ 4+1 cc	Neg Chol. antig.	2		I S 0		
11/24/20	Neg c̄ 4+1 cc Neg c̄ 4+1 cc	Neg Chol. antigen	6		I S 1/8		
12/6/20	Neg c̄ 4,1 cc Neg c̄ 4,1 cc	Chol. antigen	8		I S 1/6		
2/1/21	Neg c̄ 4,1 cc	Neg	6				

Fig. 14.—Chart of the Spinal Fluid and Blood Findings of a Typical Case of Asymptomatic Neurosyphilis, Recognized by Routine Spinal Fluid Examination in the Early Secondary Period. Note that treatment with arsphenamin alone did not control the progress of the meningitis, and that a good result was obtained only after intraspinal treatment was begun. Slight rises in cell count, regardless of the spinal fluid Wassermann reaction, may be of serious significance early in the course of syphilis. Note, too, that the blood Wassermann reaction (right-hand column) was negative much of the time while the neurosyphilis was progressing.

Local Treatment of Syphilids

In early syphilis, the treatment of local lesions is summed up by saying that it is unnecessary if an effective systemic technic is adopted. The occasion should not pass, however, without emphasis on the inexcusableness of locally treating a genital lesion without first making every effort to reach a diagnosis by the use of the darkfield. There are few commoner syphilologic sins among the profession at large, even to-day, than this. No genital lesion should receive any local application other than physiologic sodium chlorid solution until it has been searched repeatedly for spirochetes. If the Spirochæta pallida is found, treatment for syphilis will induce a prompt involution of the lesions unless there is a complicating factor such as a Vincent symbiosis (gangrenous balanitis) or an unusually virulent chancroidal infection. In such cases, hot soakings in potassium permanganate, 1 : 4,000, with irrigations under the foreskin with a soft rubber syringe, if there is phimosis, will hasten involution. The mutilating dorsal-slit operation is usually unnecessary and often results in extensive gangrene. If there is contraction of the opening in the prepuce after the lesion has healed, a proper circumcision may be done.

Excision of the primary lesion should never be practiced as a therapeutic measure. I have even ceased to advocate it in patients supposedly cured because, if patients sustain a recurrence in the scar, they will probably sustain one in some focus elsewhere in the body which, although invisible to the examining eye, is none the less real from the standpoint of relapse. Most secondary lesions require no local treatment. Even an extensive rupia involutes with amazingly little residuum under efficient systemic measures. It may increase the patient's comfort to remove the crusts and apply a wet compress of permanganate solution or dilute bichlorid (1 : 2,000) until the base is clean. There is no excuse for local treatment of mouth and throat lesions when they can be swept away almost miraculously with arsphenamin.

Extensive late syphilids of the skin at times require local measures, especially wet dressing with boric solution or aluminum subacetate (0.5 per cent) to hasten their involution. Small autogenous clipped grafts may be used after treatment is well under way. This is rarely necessary, however. The amount of deformity is always much less than is expected.

Osseous syphilis must at times be treated locally by the removal of sequestra, as previously mentioned. Fluctuating gummata may be drained provided treatment has been begun. In all cases in which surgical intervention might seem advisable, it should be recalled that tissue restoration in a syphilid is always better than the gross appearance of the lesion would lead one to expect, and intervention should not be made until weeks or months of systemic treatment has arrested the process.

CONCLUSION

The urgent need of modern syphilology is for a boiling-down to essentials and less roaming of the human experimental field. For early syphilis, prompt diagnosis, immediate continuous combined treatment, carried out systematically to a maximal standard of two to three years irrespective of all speculative considerations of cure, and followed by lifelong observation for relapse, are the cardinal essentials. For the fully established infection, the prophylactic viewpoint, both as regards the potential carrier and the possibilities of complications, a high degree of individualization, and lifelong observation are the essentials. It is impossible to split the field of syphilotherapy into air-tight compartments, each labeled with a diagnosis and a formula to be applied. In the long run, that technic of management in syphilis which perfects the phase of observational control will best know and right its errors, will have the fewest complications, and will contribute the most to our control over the disease. It is in the development of this phase of observation that the practitioner in the field and the syphilographer at the advisory center will find many as yet undeveloped opportunities for coöperation.

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CHAPTER XXXII

WEIL'S DISEASE (SPIROCHÆTOSIS ICTEROHÆMORRHAGICA)

George Blumer

The investigations of the Japanese observers, Inada and Ido, and of physicians attached to the various armies engaged in the Great War have made it clear that there is a type of infectious jaundice due to spirochetes which corresponds clinically to Weil's disease. Investigations conducted in the United States have demonstrated that this is not the only form of infectious jaundice and there is good reason to believe that the non-fatal type of infectious jaundice which has been so commonly observed here in the past few years is not spirochetal in origin.

True Weil's disease, spirochetosis icterohæmorrhagica, is a common disease in certain parts of Japan and prevailed extensively among the various armies engaged in the late War. In times of peace it is undoubtedly endemic on the continents of Europe, Asia, Africa and South America, and, judging from available clinical records, probably occurs at times in North America.

The disease is due to an organism, described by Inada and Ido as Spirochæta icterohæmorrhagiæ, very similar to the Leptospira icteroides of Noguchi which causes yellow fever. Noguchi suggests that the name Leptospira icterohæmorrhagiæ is preferable to the original designation of Inada and Ido. The organism is an anaërobe, is easily cultivated on artificial media and is readily transferable to certain laboratory animals, such as the guinea pig, in which it produces characteristic jaundice. In human beings the organism is probably constantly present in the blood during the first week of the disease and persists for much longer periods in the urinary system, having been found in the urine of some patients at least two months after the onset of the infection. It may be demonstrated at times in the centrifugalized blood-serum by means of darkfield illumination, and intraperitoneal inoculation into guinea pigs of 2 to 3 c.c. of whole blood taken early in the disease yields a large percentage of positive results (Gwyn).

In the transmission of the disease the rat plays an important rôle, the organism being excreted in large quantities in the urine of infected animals. In the late War the majority of infections occurred among front line troops and the very common infestation of the trenches by rodents is doubtless the explanation of this. There is some evidence that insect vectors may play a minor rôle in transmission, but most of the common biting insects are incapable of conveying the spirochetes and the common method of infection is probably through food or water contaminated by rat urine.

The period of incubation, according to the Japanese observers, is about one week.

The symptomatology is quite characteristic in most instances, though cardinal signs, such as the jaundice, may be lacking. The onset is usually extremely abrupt with chill, fever, prostration, severe headache and pronounced muscular pains. Symptoms of gastro-intestinal irritation are frequent at the onset. Nervous manifestations are common. In addition to the headache and prostration mentioned, vertigo, somnolence, muscular twitchings and in severe cases convulsions and coma may occur.

The fever is generally high, from 102° F. to 104° F., and shows little variation for the first nine or ten days. After this period it gradually falls by lysis, to be followed in many patients after three or four days of apyrexia by a recurrence ordinarily lasting from three to six days and occasionally much longer.

The physical signs of greatest importance are the jaundice and the hemorrhagic manifestations. The jaundice does not usually occur before the third day and may not be apparent before the end of the first week. It is not usually very deep and is of an orange rather than a yellow hue. It usually disappears with the subsidence of the fever. With the jaundice skin eruptions of an erythematous or a macular type are not uncommon. The conjunctivæ are deeply injected and herpes labialis, which may be hemorrhagic, is common.

The hemorrhagic manifestations may take the form of nose-bleed, of blood-stained sputum, of melena, of hemorrhages from the gums or of hematemesis. Microscopic blood in the urine is not uncommon.

Other signs of less importance are bronchial râles, enlargement and at times tenderness of the liver and spleen, and marked albuminuria and cylindruria. The enlargement of the spleen is not apparent in more than 10 per cent of the patients and the urinary changes are usually febrile and irritative rather than indicative of a true nephritis. The leukocyte count may be normal or a moderate leukocytosis may be present, 11,000 to 17,000 cells per cubic millimeter, usually with an increase in the polymorphonuclear cells. Severe anemia seems to be unusual.

The mortality of the disease in European countries is about 4 or 5 per cent according to Dawson, Hume and Bedson. In Japan the mortality is much higher, 32 per cent of the patients succumbing in some outbreaks. The picture of icterus gravis is usually present in the fatal cases. Complications are few but convalescence may be prolonged.

Prophylaxis.—Inasmuch as the rat plays an important rôle as a carrier of infection, the extermination of rodents in endemic or epidemic foci is of importance, the problem in this respect being similar to that in plague outbreaks. Equally important is the protection of food and water supplies from contamination with the urine of rats. As the organism may be excreted in large numbers in the urine of patients, and possibly in other discharges, all excreta should be carefully sterilized as in a case of typhoid fever. Clothing and bedding should be punctiliously sterilized by means of heat or the usual chemicals. Nurses and others coming in contact with patients should observe the technic of an infectious ward. Gowns should be worn and strict attention should be paid to proper cleansing of the hands, especially before meals. In the present state of our knowledge special protection against biting insects seems superfluous.

Treatment.—There is no specific treatment and no effective chemotherapy. Inada and his coworkers did some experimental work on serotherapy which indicated that little could be expected when the disease was fully developed. On the grounds of analogy it might have been expected that arsphenamin would be of value but Inada's experimental work was inconclusive and Dawson, Hume and Bedson state that the drug is valueless.

The treatment is therefore that of an infectious fever with special attention to harassing symptoms. The patient should be kept in bed in a well-ventilated ward or room. Free water drinking should be encouraged or, if vomiting precludes this, the introduction of fluid through saline enemata, the Murphy drip, or even intravenous infusion in severely toxic patients may be demanded. Dawson suggests the use of an alkaline mixture.

The diet should be soft, easily digested and poor in fats and proteins. Many of these patients lose weight rapidly and for this reason an attempt should be made to introduce an adequate number of calories daily. The occurrence of gastro-intestinal irritation may make this difficult at the onset of the disease. The food should be non-irritating and the protein content should be low, as renal function is often depressed. Fats must be given cautiously and in the most digestible form.

A preliminary purge may be desirable, but after it has acted the bowels should be moved by salines or preferably by daily enemata. On account of the irritable gastro-intestinal tract repeated severe purgation is to be avoided.

In the early stages of the disease the headache and muscular pains may be very severe and sedatives may be needed to allow of the proper amount of rest. The ice-bag to the head may be of value and mild sedatives like phenacetin and salol are preferable to the opiates. Weil suggests antipyrin subcutaneously in doses of gr. 3½ (gm. 0.2). Codein or even morphin may be needed in patients with very severe pain.

Convalescents should receive a liberal diet with rest and outdoor life. Change of scene may, as Ramsay suggests, be valuable in patients whose convalescence is protracted.

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CHAPTER XXXIII

RAT-BITE FEVER

Wilder Tileston

Synonyms.—Sodoku, Rattenbisskrankheit, fièvre par morsure de Rat.

Definition.—Rat-bite fever is an infection characterized by relapsing fever following the bite of a rat, and due to the Spirochæta morsus muris (Futaki).

History.—Rat-bite fever has been known for centuries in Japan. Scattered case reports are to be found in the American, Scotch and French literature of the last century, the first case in this country being reported by Wilcox in 1840. An excellent clinical description was published by Miyake, a Japanese, in 1900. Since then cases have been reported from all parts of the world. Hata, in 1912, introduced treatment by arsphenamin. The causative organism was discovered by Futaki, Takaki, Taniguchi and Osumi in 1915.

Rat-bite fever is not an excessively rare disease, as the increasing number of case reports in the literature shows. The writer has seen 4 cases in New Haven within the past eight years, 2 of which were published.

Good clinical descriptions are to be found in articles by Miyake and Crohn. Blake gives references to the literature up to 1916, and Arkin up to 1920. Up to the latter date about 130 cases had been reported.

Etiology.—The disease is caused by infection with the Spirochæta morsus muris. This is a small, actively motile organism, rather thick, 2 to 5 microns in length, with flagellæ at both ends. It presents about one spiral for each micron of length. Including the flagellæ it measures from 6 to 10 microns. It is readily stained by aniline dyes, and by the usual stains for spirochetes. It is Gram-negative.

The organisms are detected with difficulty in the blood and tissues of human cases, but are readily demonstrable by animal inoculation of blood or tissues, the most favorable subjects being white mice.

Cultivation has been successfully practiced by Futaki.

The Experimental Disease.—White mice, guinea pigs and monkeys are the most susceptible animals. In white mice and rats the organisms multiply and persist indefinitely in the blood, but the animals do not sicken. In the guinea pig and monkey a disease more or less similar to that in man can be produced. Guinea pigs when bitten by infected rats contract the disease, and invariably die within a period of two weeks, the principal symptoms being fever and emaciation, with loss of hair. The disease can be transferred to other guinea pigs ad libitum by inoculation of blood or tissues. In the case of the monkey, Ishiwara was able to reproduce all of the features of the disease as seen in man, including the rash.

The spirochetes are present in from 3 to 12 per cent of wild rats in Japan, as shown by Ishiwara and others. They are not found in the saliva of the rat, but are very numerous in the blood, so that infection probably takes place from inoculation of the rat's blood during the act of biting, owing to abrasion of the gums. This explains why several people may be bitten by the same rat, but only one may contract the disease.

Immune (spirocheticidal) bodies have been demonstrated in the blood of convalescent patients, and experiments by Kusama have shown that one attack confers immunity.

Various other organisms have been described as the cause of rat-bite fever. In cases where the typical incubation period, recurrent fever and eruption have been present, it is probable that the findings were due to mixed infection or to contamination. In the case of the streptothrix, however, more discussion seems necessary. Schottmüller, Blake, Tunnicliff and Litterer have cultivated a streptothrix from the blood, and this organism was found in the tissues in 2 fatal cases. Tunnicliff has found a similar streptothrix in the lungs of white mice dying of bronchopneumonia. Blake's case, however, did not show the typical course of rat-bite fever, and some of the others are imperfectly described. It seems probable, therefore, that following the bite of a rat either true rat-bite fever or streptothrichosis may develop. Sporotrichosis has been reported by Moore and Davis following the bite of a field mouse.

Rat-bite fever follows the bite of a wild rat, or of animals which have bitten rats, such as cats or ferrets. White rats and mice are not infective. The disease is transmitted only by biting. It occurs at all ages and in both sexes.

Pathology.—The postmortem appearances, as shown by Kaneko, consist of hyperemia and degenerative changes in the kidneys and liver, and hyperemia of the meninges. The regional lymph-nodes show marked hyperplasia of the follicles, with hemorrhages and infiltration with polynuclear leukocytes. Similar changes are encountered in the bitten area. Spirochetes have been found in the regional lymph-nodes, the skin eruption, the kidneys and adrenals, and once in the testicle.

The lesions in the experimental disease are similar to those in man.

Symptomatology.—There is an incubation period, lasting usually about two weeks, and ranging from two to thirty days, during which the bite heals and there are no symptoms. At the end of this time the seat of the bite becomes swollen, red and painful. Sloughing and gangrene sometimes set in, but suppuration does not occur, in the absence of mixed infection. The lymphatics which drain the wound become swollen and tender, with redness of the overlying skin, and the regional lymph-nodes are enlarged and painful.

In a few days the first paroxysm of fever sets in. The temperature rises rapidly to 103° or more, with symptoms of toxemia, and an erythematous rash appears. After a duration of from six hours to five days, the temperature falls by crisis, with sweating, the signs of inflammation subside and the patient feels well until the next paroxysm. In typical cases the attacks recur with remarkable periodicity every three to eight days, the free intervals becoming longer as convalescence approaches.

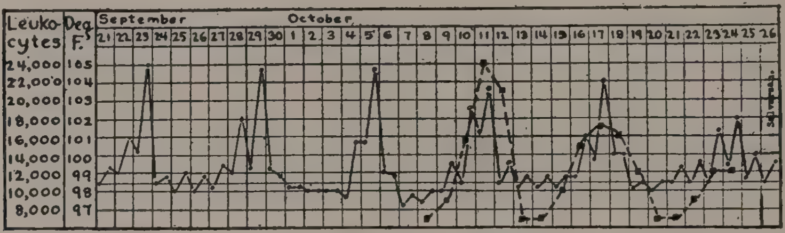

Fig. 1.—Temperature and Leukocyte Chart: Solid Line, Temperature; Broken Line, Leukocytes. Tileston Journ. Am. Med. Ass., lxvi, 995, 1916.

Fresh inflammation appears in the wound and the lymph-nodes with each attack, to subside during the interval.

During the seizures there is often dysphagia, which may be very distressing, the throat is sore and may be the seat of an erythematous rash, and the voice is husky. Muscular pains and tenderness, sometimes associated with induration, are very common, with a tendency to localization in the sterno-mastoid muscles. Nausea and vomiting are common.

Nervous symptoms are frequent, ranging from paresthesias and neuralgic pains to delirium, stupor or coma.

The Rash.—An eruption, which is of great diagnostic importance, appears in the majority of cases. It may be either local or general. The former occurs as a diffuse bluish red erythema of considerable extent, with well-defined margins. It is situated at the seat of the bite, and also in the skin overlying the lymph-nodes which drain the wound.

The generalized form of eruption, when typical, is almost pathognomonic. It consists of fairly numerous bluish-red spots, circular in shape, slightly raised, with sharply defined margins. The size varies from that of a pea to a silver dollar (0.5 to 3 cm.). In the course of a few days they fade in the center and become ring-shaped, resembling the lesions of erythema multiforme, but differing from that disease in that they show no predilection for the extensor surfaces. They are seen on the face, trunk, and extremities. They do not itch, and seldom desquamate. They do not entirely disappear during the afebrile period, and become bright again with each succeeding bout of fever, when new spots may appear.

Physical examination is otherwise essentially negative. There is no generalized enlargement of the lymph-nodes, and the spleen is seldom palpable. Endocarditis does not occur in uncomplicated cases. Rigidity of the neck is occasionally present, the spinal fluid showing increased pressure and a moderate increase in the cell count, with lymphocytosis, as noted by Costa. The tendon reflexes may be exaggerated.

The blood shows a marked polynuclear leukocytosis during the attacks, the count returning to normal in the intervals. There may be a secondary anemia of moderate degree. Spirochetes are rarely to be found in blood smears, but can be demonstrated by animal inoculation. The Wassermann reaction is sometimes positive, becoming negative after treatment; it is usually negative.

Clinical Course.—In addition to the usual relapsing type, there is one with continuous fever, and an afebrile form. The former lasts a few weeks and often ends fatally; rarely it is followed by a series of paroxysms. The afebrile form is characterized by the appearance of the local signs of the disease and malaise without fever; the eruption if present remains localized.

The usual duration of the relapsing type is several months, but in Japan cases have been reported which lasted much longer, up to seventeen years. In such cases the intervals are longer, as much as a month. Very rarely there is only a single bout of fever.

Complications.—Acute nephritis is a common and sometimes fatal complication, occurring in 17 per cent of the cases collected by Crohn. It is probably due to localization of the spirochetes in the kidneys.

Diagnosis.—Rat-bite fever should be suspected in any case of recurrent fever in which relapsing fever, trench fever, and the relapsing form of Hodgkin's disease can be excluded. In such a case a history of a bite by a rat or by animals that associate with rats should be inquired for.

From relapsing fever it is distinguished by the history of a rat bite, the local signs and the eruption. The spirochete of relapsing fever may be found in great numbers in the blood, while that of rat-bite fever is seldom directly demonstrable.

It differs from ordinary sepsis following rat bites in the presence of a considerable incubation period, the periodicity of the fever, and the rash. Streptothrichosis and sporotrichosis may be recognized by cultural methods.

Inoculation of the patient's blood or lymph-nodes into a white mouse, either into the peritoneum or subcutaneously, usually yields positive results, especially during the febrile period. The spirochetes appear in the blood of the mouse after an interval of from seven to thirty days.

The therapeutic test offers valuable evidence, any case resisting arsphenamin being almost certainly not rat-bite fever.

Prognosis.—The prognosis in untreated cases is fairly good, the mortality being about 10 per cent. Death occurs most often in the type with continuous fever, or in infants and the aged as a result of anemia and exhaustion, or terminal bronchopneumonia.

Treatment.—Prophylaxis is important, for according to Miyake immediate cauterization of the wound with phenol or the actual cautery is a sure preventive. Medical treatment of the disease was unsatisfactory up to 1912, when Hata introduced the use of arsphenamin with brilliant results. It may be stated positively that arsphenamin is a sure cure for rat-bite fever, if used in sufficient dosage. It may be given either as arsphenamin or as neo-arsphenamin, in the same way as in syphilis. Occasionally a single dose is curative, but it is better to give two or three injections after the cessation of the symptoms. Relapses are unusual in well-treated cases; they can be controlled by further injections.

The prophylactic use of arsphenamin would undoubtedly be effective and might be tried in selected cases.

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CHAPTER XXXIV

BRONCHIAL SPIROCHETOSIS

WILDER TILESTON

Synonyms.—Bronchospirochetosis, bronchopulmonary spirochetosis, hemorrhagic bronchitis of Castellani, Castellani's bronchitis.

Definition.—Bronchial spirochetosis is an infectious disease affecting the bronchi and sometimes the lungs, caused by the Spirochæta bronchialis Castellani. It is in the main a tropical disease, but occurs at times in temperate climates.

History.—The disease was first described by Castellani in 1906, in Ceylon. His observations were soon confirmed by Branch in the West Indies and Chamberlain in the Philippines. It has since been found in various parts of Africa and Asia, in South America and in Europe. Violle, in 1916, observed a French epidemic at Toulon, resulting from the importation of native troops from the Far East. Cases have been reported in the United States by Rothwell, Mason, Levy, and by Bloedorn and Houghton, some of them occurring in persons who had never been out of the country. An excellent description with references may be found in Castellani's and Chalmers' *Manual of Tropical Medicine,* and there is a good critical review by Salomon.

Etiology.—The causative organism is extremely polymorphous, showing short and long, thick and thin forms, with tapering ends. The number of spirals varies from two to eight, and the length from 5 to 27 microns. It is actively motile, but loses its motility rapidly after removal from the body. The motile stage, as shown by Fantham in his excellent detailed description of the organism, is succeeded by a resting phase in which granules or coccoid bodies are formed, from which new spirochetes develop. Multiplication also takes place by transverse fission. It does not stain well with the ordinary dyes, but may be demonstrated by the Fontana silver nitrate method, by Giemsa or any of the modified Romanowsky stains, or by dilute carbol fuchsin. Attempts at cultivation have failed. Successful inoculation has been performed only by Chalmers and O'Farrell, who were able to infect a monkey. The lower animals are immune.

The spirochetes are found only in the sputum, being absent from the urine and blood. Infection probably takes place by inhalation of the organisms which have been expectorated, but might also occur indirectly through soiled linen.

Most authors regard it as a specific organism, but Delamare and others have maintained that it is frequently associated with fusiform bacilli, and that it is identical with Vincent's spirillum. The usual absence of fetor and fusiform bacilli and the morphology are against this view, but it is possible that some of the cases have been due to infection with Vincent's organisms.

Pathology.—The pathology is uncertain on account of the absence of autopsies in uncomplicated cases.

Symptomatology.—Two forms are encountered, the acute and the chronic.

The Acute Form.—The acute form is ushered in by chilliness, fever, malaise, headache and pains in the back and limbs. The fever is usually moderate, and lasts from a few days to several weeks. There is frequent cough, which may be paroxysmal, with retrosternal pain. The sputum is at first mucous, then mucopurulent and often blood-streaked; it is usually odorless. For periods of a few days, and this is especially characteristic, it becomes pink and jellylike, and true hemoptysis may occur. There may be night-sweats, so that tuberculosis is strongly suggested. Prostration and loss of weight may be slight or marked. Relapses are rather frequent. In subacute cases fever may be absent. Physical examination shows only the signs of bronchitis, or occasionally small areas of bronchopneumonia.

Beau, Dide and Ribereau noted a fetid form in which the onset was acute with very high fever and prostration; the sputum was bloody and ill-smelling and contained numerous spirochetes and sometimes fusiform bacilli.

The Chronic Form.—Chronic bronchial spirochetosis usually has an insidious onset, but it may begin with one or more acute attacks. Over a period of months or years there is cough with mucopurulent sputum which is frequently blood-streaked; repeated attacks of hemoptysis, usually small in amount, may occur. The general condition is frequently quite good, though marked wasting is met with in a few cases. The temperature may remain normal or there may be an irregular fever of low grade. Periods of improvement are common. This form closely simulates chronic pulmonary tuberculosis.

The findings on physical examination are meager, and are confined to the lungs. Usually only a few moist or dry râles are found, located chiefly at the bases of the lungs; occasionally there are small areas of consolidation. The radiologic examination is usually negative, except for some peribronchial thickening. The sputum is free from tubercle bacilli, and shows spirochetes, often in great numbers and unaccompanied by bacteria. Fusiform bacilli have been associated in a minority of the cases. The sputum is usually odorless.

The blood shows little out of the ordinary, either in the acute or the chronic form. There may be a slight anemia. The total leukocyte count is normal or somewhat reduced, the differential count is normal, or there may be a moderate lymphocytosis.

Nolf has described a fetid spirillar bronchitis which is probably distinct from bronchial spirochetosis, differing from it in the more severe clinical course, and in the characteristics of the sputum, which is very fetid and usually free from blood. He regards the spirochetes found by him as distinct from Vincent's spirillum and Spirochæta bronchialis.

Complications.—Tuberculosis of the lungs may be associated and, in China, according to Faust, this is often the case. In the tropics complication by bronchomycosis has been observed, though rarely. In Mason's case there was pyopneumothorax, and spirochetes were present in the empyema fluid.

Diagnosis.—In patients with a history of repeated hemoptysis or blood-streaked sputum, who are in good physical condition and show only the signs of bronchitis, a suspicion of bronchial spirochetosis may be entertained. The sputum should be examined after careful cleansing of the mouth and throat to exclude contamination with mouth spirochetes. Either darkfield illumination or one of the stains mentioned above may be used. Diagnosis is made on the presence of the Spirochæta bronchialis in the sputum and the absence of tubercle bacilli, with negative roentgenological findings. It should be borne in mind that the two diseases may coexist. The therapeutic test, rapid improvement with disappearance of the spirochetes following the administration of arsenicals, offers further confirmation.

Acute cases may be confused with influenza, malaria, or tuberculosis. The chronic form is usually mistaken for tuberculosis. Other causes of hemoptysis, such as bronchiectasis, aneurysm and mitral stenosis, should be excluded. In the tropics, parasitic hemoptysis or infection with the lung fluke (Paragonimus ringeri) must be considered. It is readily recognized by the presence of the operculated ova in the sputum.

Prognosis.—The prognosis is favorable for life, no deaths having been reported in uncomplicated cases. The acute form tends to spontaneous recovery, though relapses are frequent and the disease may become chronic.

Treatment.—Acute cases often recover on simple rest in bed. Arsenical preparations, and especially arsphenamin, are of great value, as in various other diseases due to spirochetes. In Bloedorn and Houghton's 3 cases, prompt recovery followed intravenous injections of neo-arsphenamin in the usual dosage. The injections should be continued for some time after the disappearance of spirochetes from the sputum, on account of the tendency to relapse. Fowler's solution and injections of sodium cacodylate are also recommended. Castellani states that tartar emetic, combined with Fowler's solution or iodids, is useful in certain cases. Farah reports favorably on the use of intramuscular injections of iodin.

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CHAPTER XXXV

INFECTION WITH FUSIFORM BACILLI AND SPIROCHÆTÆ

William R. Williams

Synonyms.—Plaut's angina, Vincent's angina; ulceromembranous stomatitis, ulcerated gums, acute pyorrhea alveolaris, noma.

Definition.—Infection with Bacillus fusiformis and Spirochætæ is an inflammation of the mucous membranes or skin with more or less necrosis of tissue and consequent ulceration and with the presence in the necrotic membrane of certain fusiform bacilli and spirochetes.

We have as yet no satisfactory name for this disease. Its various manifestations have each of them received names that apply well enough to a single site of infection, but no general term has been accepted. The lesion is essentially a necrotic inflammation that may be mild or severe. The necrosis of tissue when superficial causes a faint pseudomembrane; when very severe it constitutes noma, although it has not as yet been shown that all cases of noma are due to this infection. The dead tissue may slough off or disintegrate, leaving an ulcer. The deeper ulcers are craterlike. The mouth and throat are most frequently attacked. The gums are much swollen and spongy and bleed readily. The tonsils show a false membrane spotted or continuous, of a grayish or darker color, that may be replaced by ulcers. The cheeks may show patches. The lesions may spread superficially or deeply and in the severest cases assume the character of noma. The cervical nodes are moderately swollen but rarely necrose. The condition is occasionally seen on other surfaces such as the genital mucous membranes. The extent to which it may extend upward from the anus, or downward from the mouth, is a matter of discussion.

In the lesion, especially in the border zone between living and necrotic tissue, are found the specific organisms of the disease. They are (1) Bacillus fusiformis and (2) Spirochætæ. The fusiform bacillus is rather large, fusiform in shape and is stained without much difficulty. The spirochetes show a variable number of somewhat irregular twists. They stain with greater difficulty than the bacilli. Sometimes one or other of these organisms predominates in direct smears from the lesions, but both are usually present in large numbers, especially when the material is obtained from the deeper areas of necrosis. The relation between these two forms is still a matter of dispute. Some bacteriologists claim that they represent different stages in the growth of a single organism, others that they are entirely separate forms, but grow more or less symbiotically. An absolute demonstration of their causative relation to this disease has not been made, although it is the prevailing view that their presence in abundance in the lesions establishes the diagnosis, particularly when diphtheria and syphilis are excluded.

The most frequent site of attack is the mouth and throat. Frequently the first symptoms are those of gingivitis, later, and very commonly, one or both tonsils are attacked and present an appearance resembling more or less closely a luetic or diphtheritic throat. The pseudomembrane may be brushed off with some difficulty and a bleeding surface left. The breath is fetid. Salivation is present. The fever varies in height, as do constitutional symptoms. The course of the disease is apt to be protracted over a period of a few weeks, or, with exacerbations and remissions or intermissions, over a period of months. The pseudomembrane may be dissolved or sloughed off, leaving ulcers that may be rather deep and sharply defined. In the more severe cases, the necrosis and ulceration assume the character of noma. On the other mucous membranes of the body analogous appearances are found. The cervix uteri, the vagina and the vulva present these lesions rather infrequently.

The list of occasional complications is a very long one and includes otitis media, mastoiditis, meningitis, infections of the nasal sinuses, brain abscess, bronchopneumonia, abscesses of the liver and spleen, or even a general pyemia with multiple abscesses.

The *prognosis* as to life is on the whole good, although the severest cases may be fatal. The diagnosis is based on the exclusion of diphtheria and syphilis and upon the presence in direct smears from the lesions of the specific organisms of this disease.

Prophylaxis.—The disease seems more common among persons in unsanitary surroundings and in the absence of personal cleanliness. It was met with frequently in the armies during the late War. Therefore, it would seem that ordinary careful hygiene of the mouth and teeth is a good preventive.

The disease is doubtless communicable from one patient to the next, although the organisms are commonly present in many mouths never attacked. It is wise to disinfect the saliva of patients and materials contaminated by the discharge from the mouth or the lesions elsewhere. Personal cleanliness of other parts of the body is effective in lessening the incidence of the disease there.

Treatment.—The use of arsphenamin or neo-arsphenamin is usually followed by a striking improvement in the condition, which lasts for a few days, but not infrequently it is followed by a recrudescence. The drug is administered intravenously in maximum doses of 6 dg. of arsphenamin or 9 dg. of neo-arsphenamin. In younger patients, or those to whom one fears to give this large dose, smaller doses may be given at first. In the mild cases a single injection may suffice. The patient should, however, be kept under close observation and the drug should be repeated whenever signs of a recrudescence appear. In the severe cases the dose may be repeated at intervals of five days or a week until the disease is under control. The neo-arsphenamin has been successfully administered by intramuscular injection. The administration of these remedies seems by far the most efficient treatment, but, in addition to this, local treatment is usually resorted to. The great number of remedies used in treating the disease locally testifies to the disappointments met with in their use. The lesions may be swabbed with solutions of arsphenamin, 1 dg. in 20 c.c. of distilled water alkalinized as for intravenous use, or neo-arsphenamin, in about the same strength of solution. Other remedies for local application are tincture of iodin in full strength, Lugol's solution, aqueous solutions of silver nitrate (2 to 6 per cent), chromic acid (10 per cent), zinc chlorid (2 per cent), argyrol (10 to 20 per cent), potassium permanganate and many others, either astringents or caustics. Patients have recovered after the use of one or several of these remedies. When the disease attacks the gums, careful treatment by a dentist is of service. Similar local applications may be made to the lesions at whatever part of the body they may occur. The local application should be repeated daily when the stronger and more caustic solutions are used, or several times a day when the weaker solutions are used. In addition to this, bland mouth washes, such as the alkaline antiseptic solutions, may be used frequently to lessen the fetor of the breath and to add somewhat to the patient's comfort. The general treatment of the patient depends upon the severity of his symptoms. The more severe cases are kept in bed, the mildest cases are allowed to go about. The diet is governed by the ability of the patient to swallow. It may need to be restricted to liquids when the throat is quite sore, but no advantage is to be gained by underfeeding. In fact, inasmuch as the disease is often protracted, it is important to give the patient enough to eat. Milk, eggs and cream may usually be given in adequate amounts to nourish the patient sufficiently. Recrudescences and recurrences should be looked for and should be treated vigorously at the onset. When the infection tends to persist in the tonsils, tonsillectomy should be resorted to.

INFECTIONS DUE TO METAZOA

CHAPTER XXXVI

INTESTINAL PARASITES

F. Forchheimer

Revised by George Blumer

ASCARIASIS

Ascaris Lumbricoides

Infection takes place by means of the ova, which are produced in great numbers and which, by feeding experiments, have been shown to produce ascariasis in the human being. The ova retain their viability under conditions usually fatal to lower forms of life, and adhere to food for a great length of time; they have been found in water and upon various articles of food, especially vegetables that have been grown in manured soil. The temperature of boiling water destroys them.

The normal habitat of this nematode is the small intestine. But these worms are wanderers, being found in the esophagus, the mouth and the larynx, in hepatic abscesses, in the large biliary ducts, and in the appendix. Wherever they are found, they act as an irritant either mechancially or chemically, or in both ways. The recent work of Stewart and others shows that the larvæ frequently wander into the lungs and are probably responsible for some forms of pneumonia in children.

Prophylaxis.—The prophylaxis is practically summed up in obtaining a pure water supply, and where this is not possible boiling of liquid foods and all vegetables given to children. Young children should be prevented from fouling their hands with soil which has been contaminated by the feces of pigs or human beings. They should also be educated to keep their hands out of their mouths, and should never be allowed to eat without first thoroughly washing their hands. Auto-infection from ova is not common in ascariasis.

Treatment.—As many symptoms are ascribed to intestinal worms, the diagnosis should invariably be established before treatment is instituted; this can always be easily done by a microscopical examination of the feces, for the ova, when ascarides are present, are plentiful and characteristic.

Even when one worm has passed, a little time should be allowed to elapse, after which the feces are again examined, and the presence of the ova will show the necessity of treatment. In pursuing this method it is frequently found that further treatment is unnecessary because only one worm was present. As the Ascaris lives only in the small intestine, the treatment is applied by the mouth exclusively; the only remedy required is santonin. But santonin is not a harmless drug, and whoever, like myself, has seen fatal santonin poisoning in a case in which there were no worms will be very cautious in its use. In children as small a dose as 0.13 gm. (gr. ij) has been followed by death; in adults 0.3 gm. (gr. v) has produced symptoms of serious intoxication. In children the dose should be small, not to exceed 0.02 gm. (gr. 1 to 3)—not more than 0.065 gm. (gr. j) in twenty-four hours; in adults 0.065 gm. (gr. j)—not more than 0.3 gm. (gr. v) in twenty-four hours. The administration of santonin to children in the form of worm lozenges should not be encouraged; they are looked upon as delicacies by the little patients, with the result that too many are taken, to say nothing of the harm done by promiscuous domestic medication. Santonin has little taste, so that the addition of a little sugar suffices to make it palatable. It should always be given together with a laxative, as in this combination the local effect is not impaired and the general effects are, in a measure, diminished by it. The best laxative for our purpose is calomel; I always combine the two and always give a prescription calling for not more than three powders. Liebreich has recommended castor oil in combination with santonin; the objections to this method in childhood are quite obvious, though it is very efficient.

On account of the risks of producing unpleasant symptoms, santonin should never be given for diagnostic purposes, as is often recommended. Causal treatment is paramount, and for those symptoms due to the wandering of the Ascaris local therapy is necessary.

In recent years oil of chenopodium has been widely employed as a remedy for ascariasis. The technic of its use is as follows: The evening preceding treatment the patient is given a light meal and this is followed by a purgative dose of magnesium sulphate. The next morning a light breakfast of milk is given. The oil of chenopodium is given in 3 doses, each 0.5 c.c., at 7, 8 and 9 A.M. The drug may be given on sugar or in freshly prepared capsules. At 11 A.M. a purgative dose of magnesium sulphate is given. Unfortunately the same objection can be made regarding chenopodium as was made regarding santonin—toxic symptoms may occur.

It is claimed that the ascaris produces a toxic body during its activity in the small intestine, which is absorbed and produces one or more symptoms, such as anemia, picking at the nose, nervousness, grinding of the teeth, convulsions, and many more. All this must be proved before it can be accepted. The primary etiological importance of worms has probably been much overestimated. Certainly, nowadays, no one is justified in treating patients for worms unless his diagnosis is absolutely certain, in that either worms or their ova have been found. When this is the case causal therapy should be applied in every instance, regardless of the presence or absence of symptoms. Symptomatic treatment may have to be given, either for local or general purposes.

Oxyuris Vermicularis

The complications of ascariasis must be treated as they arise. They usually demand surgical intervention and are seldom diagnosed as ascariasis as the patient presents one of three pictures: (1) obstruction of the common bile duct; (2) intestinal obstruction (from masses of worms); or (3) generalized or localized peritonitis from perforation of the intestinal wall by worms.

Prophylaxis.—In addition to the measures described under Ascaris lumbricoides, and because of the life history of oxyuris, we find auto-infection and direct infection from man to man very common. Auto-infection is the cause of difficulty in curing this disease; the young female brood, filled with ova, lives in the colon, but eventually all the worms are found in the rectum; they produce local symptoms, especially itching, which on their part are followed by reactions resulting in the transportation of ova by means of the hands, towels, and sponges. Heller says that a microscopical examination of the accumulations under the finger nails of the patients will usually demonstrate the presence of ripe ova. Transmission of ova by fruit or vegetables, according to this observer, is of secondary importance, least of all by salad, as vinegar destroys the ova. To prevent transmission and auto-infection the most scrupulous cleanliness of the anus and vulva, as well as of the hands of the patient, is demanded. The latter is very difficult, in children especially, and not easy in adults, for infection takes place during sleep by scratching, rubbing, or mere contact with the anus or vulva. For these reasons closed drawers should be worn night and day. The finger nails should be trimmed short. When the fingers are put into the mouth, which is done so frequently by children, a circulus vitiosus is established; the worms in the anus cause the scratching, in scratching the ova become attached to the fingers, these ova are put into the mouth, and we have renewed infection. Cleaning the finger nails should be looked to; according to Vix, the worms as well as their ova are easily destroyed by soap. Care must be taken to watch all infected members of the household; otherwise renewed infection will take place.

Treatment.—The treatment of pin-worms by enemata is unsatisfactory because it does not reach the source of supply. There is no doubt that enemata give a good deal of temporary relief, but they are unpleasant, must be continued for weeks to prevent relapses, and are not always practicable or efficient.

The ordinary vermifuges are not without their disagreeable features. Naphthalin has caused death, chenopodium has caused death and blindness and santonin has caused severe intoxication. In recent years German clinicians have described a phenol derivative "butolan" which is heralded by many of them as almost a specific. The drug comes in tablet form, each tablet containing 0.5 gm., and is cross-marked so that it can be broken in the middle. How long it takes to cure a case of pin-worms depends entirely upon the methods of prophylaxis and treatment that are employed, as is shown by the different results obtained by different authors. Because of the difficulties met with in carrying out these measures, we frequently find that in private practice pin-worms are not always cured.

The drug is given in doses of 0.25 to 0.5 gm. three times a day for two or three days. It is then omitted for one day during which period a purgative is given. The butolan is again repeated for two or three days followed by a purge the day after administration ceases. After a period of two weeks this process is again repeated. During this entire period most painstaking prophylactic measures must be kept up, especially scrupulous cleansing of the anal region and the wearing of bathing tights or closed drawers day and night. A sedative ointment may be applied to the anal region at night. Ochsenius recommends the following:

℞

Benzocainæ	2 gm.
Acidi Salicylici	0.5 gm.
Vaselin vel Lanolin	20 gm.

Enemata are not necessary after the first few days of treatment.

TRICHINOSIS

Prophylaxis.—As this disease is always due to infected swine, the indications for prophylaxis are perfectly simple, their execution, as in all food infections, rather difficult. If nobody would eat pork there would be no trichinosis. But general abstinence from eating pork is not to be looked for, and with proper precautions is practically unnecessary. In order to absolutely prevent the infection of hogs they should receive only grain or such food as has been cooked, and especial care must be taken so that they are not fed with offal from slaughterhouses, as is frequently done. Rats are frequently infected with the disease and care must be taken that hogs are given no opportunity for eating these rodents. The microscopic examination of pork has been abandoned both in this country and in Germany because of its great expense and its failure always to discover the disease. Under federal meat inspection hogs are inspected both antemortem and postmortem, but in small country places they are frequently used for food without such inspection. The mode of preserving the pork seems to be most valuable for prophylaxis, as not a single case of trichinosis in Germany can be attributed to pork cured in the American manner. All food containing pig meat should be thoroughly cooked; neither ham nor pork sausages should ever be eaten raw. Trichinosis is most common where uncooked ham is eaten. But the cooking must be thorough; free trichinæ are killed at a temperature of 131° F., encapsulated trichinæ at from 190° to 200° F.; as these temperatures must be applied throughout, not only upon the surface but also in the center of the article of food, it will be seen that this method is only a partial safeguard. Yet practically Wasserfuhr has demonstrated that epidemic trichinosis is prevented by cooking, for in those regions of Bavaria where pork is always cooked no epidemic has ever occurred, while where ham is eaten raw epidemics have occurred.

The conclusions that follow the foregoing are very important.

It would seem that the American manner of curing pork or boiling it usually destroys the trichinæ. The disease is absent among those who eat properly prepared swine flesh. However, imperfectly roasted pork, insufficiently boiled ham, especially from delicatessen stores, and homemade sausages have been responsible for the disease. In this country sporadic cases and small family outbreaks are the form in which the disease usually occurs. Extensive epidemics, such as have occurred in northern Germany, are practically unknown here.

Treatment.—The purposes of treatment are twofold: (1) to remove the adult parasites from the intestines; and (2) to treat untoward symptoms as they arise.

At the time the infected pork is consumed there may be gastro-intestinal irritation, not from the trichinæ but because pork which contains trichinæ may also have undergone putrefactive changes. Brisk purgation with castor oil, calomel or salines is indicated in such patients.

The symptoms due to the entrance of the trichinæ into the system do not appear until from five days to three weeks after the infected pork is eaten. At this time most of the female adult worms are lodged in the intestinal wall where they are beyond the reach of purgatives. However, as some of the adult worms remain in the intestine, purgation is indicated at this time also. Some writers recommend in addition the standard anthelmintics, turpentine, santonin, pelletierin, cortex granati and filix mas.

There is no specific treatment which will reach the embryos once they have entered the system. There is promising experimental work that indicates the possibility of perfecting a serum which will neutralize the toxemia. Arsphenamin has been used but the reported results are conflicting.

Besides the intestinal treatment, the management of a case of trichiniasis must be symptomatic. For the diarrhea the usual treatment should be applied. Pains in the abdomen and the muscles should be met with opium; for the latter the antipyrin group, too, is valuable. For sleeplessness the usual hypnotics are used. Upon the whole, the treatment resembles that of typhoid fever, for which this disease is often mistaken; the fever, the bronchitis, the profuse sweats or complications should be treated in the same way as recommended in the previous chapters on infectious diseases. The diet should be nutritious; it is necessary to take the same precautions as in typhoid fever, as lesions are at times, though not always, found in the gastro-intestinal tract. In the milder cases very little treatment is required; in the severe cases the mortality is very great, do whatever we may. In the stage of convalescence the treatment is the same as in all other acute infectious diseases.

TRICHURIASIS (Whip-worm Infection)

The idea that infection with Trichuris trichiura (Trichocephalus dispar) is harmless has been abandoned. There is good evidence that in children it may cause serious illness and even death. The parasite is a blood sucker and its presence may be associated with frequent attacks of diarrhea with as many as twenty movements daily which may contain blood and mucus. Grave anemia may develop in these patients.

The ordinary vermifuges, chenopodium, for example, have little effect on this worm. There is a drug used in Columbia which is almost specific, the so-called "leche de Higuera." This is the sap of the higueron tree (Ficus glaborata). It is an acid syrupy substance with a styptic taste, soluble in water and glycerin but not in ether or alcohol. The method of administration is as follows:

The day preceding treatment the patient is put on liquid diet and at 8 P.M. is given 30 gm. (℥ I) of cream of tartar in a glass of sweetened water. At 6 A.M. the following morning 16 c.c. of leche de Higuera is administered in half a glass of milk. At 8 A.M. this dose is repeated. At 10 A.M. 60 c.c. of castor oil is administered. If the juice cannot be obtained fresh it may be preserved by the addition of chloroform; if this is done, however, a larger dose is required, namely, 20 to 30 c.c. According to Spruit this treatment is successful in the majority of patients.

ECHINOCOCCUS DISEASE

As the Cysticercus cellulosæ and the Echinococcus are treated in the same manner, the two subjects are discussed under one heading. They differ only as to prophylaxis, that of the Cysticercus being the same as will be found in the chapter on Tænia; that of the Echinococcus being the prophylaxis of the larval form of the Tænia echinococcus.

Prophylaxis.—For prophylaxis the first consideration must be the host for the larval form, the dog. In order that the dog does not become infected, and this refers only to infected regions, his food should be looked after, as has been described in the chapter on Trichinosis. For man the principle of prophylaxis is prevention of introduction of the embryos into his alimentary canal. These embryos are always found in the feces of the dog. Human hydatids could be prevented if the bladder worm in herbivora could be destroyed. As this is impossible, there remains the question of killing all the dogs, and this should be attempted in infected regions. For more than one reason, however, it will fail, so that we must resort to other preventive measures. The suggestion has been made to give teniacides to dogs, as is done in humans, which might do good but would necessitate disinfection of the feces. The drinking water should be boiled, vegetables should be boiled, and fruits growing low should be thoroughly cleaned before being eaten. Dogs should not be allowed to lick human beings.

Treatment.—The treatment is surgical. A glance at the localization of the echinococcus will immediately show that individualization as to mode of operation is necessary. The visceral locations in the order of frequency are: the liver, the genito-urinary apparatus, the lungs and pleura, the intestinal tract, the central nervous system, the heart and blood-vessels, the bones, and then the remaining organs. For the various operations and methods of surgical treatment the reader is referred to works on surgery.

One of these procedures must be especially referred to—aspiration—as it usually is carried out by the physician as well as the surgeon. This operation is no longer considered harmless in this disease for the following reasons: (1) Infections of surrounding tissues may follow; sudden death may occur, supposed to be due to the presence of a ptomain (Brieger) in the cyst and which is absorbed. (2) Pus infection may take place so that the patient is in a condition rendering necessary a more serious operation. (3) The therapeutic results are dubious, only favorable in living simple cysts.

A certain number of cases have been cured, either by simple aspiration or by injection into the sac of medicinal substances, such as tincture of iodin (Boinet), alcohol (Richet), corrosive sublimate (Bacelli, Sennet). Whatever is connected with aspiration is no longer favorably looked upon in the treatment of this disease.

For other intestinal parasites the reader is referred to the section on Tropical Diseases.

CHAPTER XXXVII

HOOKWORM DISEASE (UNCINARIASIS)

Samuel T. Darling

This insidious malady is not only universal amongst natives of the tropics who go barefoot but its distribution extends into the cooler latitudes from Virginia to Argentina. Among the recruits examined for hookworm in the U. S. Army the incidence was as high as 32 per cent in some states (Kofoid). The proportion of infected persons in the rural communities is greater. Not only is the disease encountered in the South but a notable number of persons infected in the southern states and elsewhere in the tropics who have taken up their residence in northern states outside of the hookworm area, have been found to harbor worms. Practitioners, therefore, should not fail to be on the alert for this infection among persons who may have lived within the hookworm area.

The disease is caused by two species of worms: Necator americanus, which is the one responsible for practically all the cases in the United States and in many other lands; and Ancylostoma duodenale, a more malignant worm encountered in association with the first-named species in Central and South America and the Orient, and found alone in Egypt and Europe and the northerly areas of endemicity in Asia.

The last-named and more malignant worm is provided with sharp piercing teeth which engage and tear the delicate mucosa in the small intestine and set up minute hemorrhages. These multiple small hemorrhages continued over long periods of years cause in an insidious manner the most profound anemia and secondary nutritional changes which ultimately may cause death or so undermine the person's health that he falls an easy victim to other and intercurrent diseases. Loss of blood very definitely is the cause of the chain of symptoms in infections with this worm.

In infections with Necator fresh blood is rarely or never encountered in the worms taken at autopsy nor in those recovered in making worm counts. This worm may exert its pernicious influence on the blood through the agency of a hemolytic toxin. Indeed both worms may possess a toxin of this nature in addition to causing hemorrhage through biting the mucosa.

Infection is in most cases slowly acquired, by larvæ entering the skin of the feet usually from infested soil which has been polluted by the excreta of infected persons. During the passage of large numbers of larvæ at one time through the skin, an itching inflammatory process may ensue known as "ground-itch." Children under one year are never infected but, as soon as they begin to run with their mates and frequent the customary places for defecation, they begin to acquire worms one by one, the number depending on the degree of soil infestation in the district. The number increases from year to year until the average number for that particular place has been reached. In towns the worm index, or average number of worms harbored by a sample of the population, is usually lower than the index of persons living in agricultural communities who are in more intimate contact with polluted and infested soil.

Men are usually more heavily infected than boys, and boys than women, women more heavily infected than girls. This is due to personal habits and to occupation. Wherever the source of infection lies, the more intimate the contact the more heavy and severe the infection. There is some difference in the amount of individual resistance to infection and to the effects of infection. Some persons became severely infected at an early age while others in the same village never acquire an unmanageable burden of worms. As a rule, however, the effects of the worm burden can be measured when cases are averaged. About eleven to twelve worms in a man will cause a drop in the hemoglobin of one point. Seven to eight worms will do the same in a boy. But this is only operative when there is a considerable burden already carried.

Small numbers of worms are as effective as large numbers in causing a loss of blood in proportion to their numbers, but this loss is easy to make up when it is small and consequently it cannot be measured by the hemoglobinometer. When intercurrent disease or another cause of anemia coexists, small numbers of worms make their presence felt. For this reason light infections should be treated in every case of intercurrent disease. Besides the anemia caused in the way just set forth, it is believed that the chronic inflammatory process which frequently is encountered in the mucosa is also a contributory cause of anemia and the intermittent fever which goes along with the more severe types of the disease.

The anemia is insidiously progressive and is probably at first of the secondary type; later, as the losses of blood fail to be compensated for, a chlorotic type of anemia supervenes. It is to be noted that the blood losses in hookworm disease are absolute, for the blood lost is carried out of the bowel in the dejecta and not stored up in the spleen and liver as in malaria, where it may be revamped. At any rate this is true of anemia caused by ankylostomes. Worms become imbedded in the mucosa of the small intestine occasionally, to be the seat of ulceration later.

In the severe cases there is pallor and anemia of the viscera and fatty metamorphosis of the heart, particularly of the papillary muscles and subendocardium of the left ventricle. The spleen is not enlarged but the yellow marrow undergoes cellular hyperplasia. Edema and atrophy are late and terminal features in severe cases due to many worms.

Hemoglobin diminishes in advance of the erythrocytes and, in recovery after treatment, lags very considerably behind the latter, the color index being always below 1.0 and often 0.5. The disease is progressive and symptoms become more and more severe. They may be divided for convenience into three groups:

A. Cases in which blood losses are compensated.

B. Cases in which compensation for blood losses is disturbed or breaking.

C. Cases in which compensation for blood losses is broken.

In the first group the cases are of light and moderate infections. There is no measureable anemia, for the blood losses are being made up. There are no well-defined symptoms, because the resistance and vitality of the patient are such that he can make good all demands. When he is subjected to an additional debilitating factor such as malaria or underfeeding he does suffer in part from the complement of worms being carried. The worm burden is usually under 100, but some persons may carry as many as 200 or 300 hookworms.

In Group B the point is about reached where the patient is no longer able to maintain a normal hemoglobin content, blood losses are not being made up, measurable anemia can be demonstrated with the hemoglobinometer, and symptoms are manifest. Heart-burn, flatulence, fullness in the stomach and epigastric pain which is relieved upon taking food are complained of. There is often a desire for unusual articles of food, such as chalk and clay. Fever is commonly intermittent, and fluctuating a degree or two above and below normal. Physical weakness incapacitates the person for arduous labor. Vasomotor disturbances bring about dizziness, accelerated pulse rate, breathlessness and palpitation on exertion. There is some dulness and indifference. The complexion becomes sallow or muddy. Members of this group are carrying several hundred worms.

In Group C, compensation for blood losses by the blood-forming organs is distinctly broken, and severe nutritional disturbances are manifest. Symptoms become intensified. Pallor of sclera, skin and mucosa is more marked. Black and brown races become ashy-colored while white and yellow races take on a waxy or tallowy color. The skin of whites is sometimes faintly tinted yellow. The subcutaneous tissue is often increased in thickness by fat and edema, giving a spuriously well-favored appearance to women and children. There is a peculiar puffy appearance in the cheeks which shake like jelly when flicked with the finger. When the edema disappears after treatment, it is seen that there has been an underlying atrophy of the tissues. Delayed puberty, menstrual irregularities and impotence are noted in this stage. Severe cardiovascular weakness and failure are manifested in hemic murmurs, palpitation, precordial pain, venous pulsation, dizziness and tinnitus aurium. Edema of legs and severe ulceration may follow trauma. There is a rather typical intermittent fever and chilliness is complained of. Physical debility becomes more pronounced, patients are easily tired on the slightest exertion, and their mental condition is often one of dulness and apathy. The terminal complex is one of extreme anemia, physical exhaustion, cardiac failure and anasarca, the hemoglobin being reduced in some cases to 10 per cent as recorded by the hemoglobinometer. Persons in this group may carry from 400 to 1,000 or more worms.

When malaria or underfeeding complicates the disease, severe anemia occurs with fewer worms, but in this case each anemia-producing factor contributes only its own quota. Practitioners should not overlook the fact that underfeeding and hard labor can contribute as causes of diminished hemoglobin and can intensify the anemia due to hookworm infection. In making the diagnosis of hookworm disease, it is absolutely necessary to know how many hookworms are being harbored by the patient. A few worms are not enough to cause severe symptoms.

The diagnosis of the presence of the worms may be made by any one of the methods of microscopic diagnosis. But whenever it is desired to know absolutely whether the worms were responsible for the symptoms, the feces should be washed and the worms counted or estimated. This may be done by washing and decantation or by washing the feces through a fine sieve (50 mesh). Very mild symptoms such as colic, epigastric distress and flatulence may be caused by a dozen or two worms but well-defined anemia with a chain of more serious symptoms can only be caused by a notable number of worms, a number hard to define because of individual resistance but which may be expressed as "several score."

TREATMENT

The administration of vermicides is not unattended with danger, for, while we possess several very effective drugs, they are for the most part either peculiarly narcotic or possess some toxic power which may be directed against a susceptible organ or the tissues of a susceptible person. The position of the practitioner is somewhat akin to that of the surgeon when called upon to give an anesthetic. He possesses several anesthetics but none of them is absolutely devoid of danger. Yet even as the surgeon does not forego the administration of the anesthetic of choice in any given case, neither should the practitioner avoid using one or more of the vermicides which have been found to possess special efficacy against the helminths which infect the intestinal tract of man rather than rely on some one of the harmless and inert vermifuges. In choosing or combining these drugs he may be reminded of their peculiar powers and warned against using them in conditions when they may be contraindicated.

At present, among physicians engaged in treating large numbers of persons infected with hookworms, certain drugs of proved excellence have come to be used exclusively. These drugs are: chenopodium oil, carbon tetrachlorid, thymol, and beta-naphthol. Other drugs such as chloroform, eucalyptus and male fern have been tried out and discarded, for, although they are harmless, they are relatively inefficient. The two first named, carbon tetrachlorid and oil of chenopodium, are fluids and aside from their specificity have a better chance of contact with the worms than the solids thymol and beta-naphthol, although the efficiency of thymol is notably increased by thorough trituration with sugar of milk.

It is customary to administer vermicides in the morning on an empty stomach. This is because of the demonstrated loss of efficiency in vermicidal power whenever food is not interdicted. Some of the vermicide becomes locked up with the food material and contact with the worms is insufficient to narcotize them and release their hold on the mucosa. It is not necessary, however, to withhold the meal of the previous evening, which may with advantage be made light.

The Purge and the Divided Dose.—With most vermicides it is necessary always to use a purge after the exhibition of the drug in order to expel it and the narcotized worms from the intestinal tract; sometimes also before the administration of the drug, to clear the intestinal tract of food residue. When, however, the dose of the vermicide is divided and given with an interval of one or two hours, the action is prolonged and the vermicidal efficiency is as good as if a purge had been given the night before treatment. Whenever it is not convenient to give a purge the evening before treatment, the dose should be divided. In any case a divided dose of a vermicide is more efficient than a single dose.

The vermicides mentioned above have been subjected to careful tests as to their relative efficiency in removing worms, and from these tests it has been determined that the drug may be rated as follows in the doses given:

DRUG VALUE WITH GIVEN DOSES

Drug	Dose	Per Cent Removed
Carbon tetrachlorid	3 cc.	98
Oil of chenopodium	1.5 cc.	95
Thymol	60 gr.	88
Beta-naphthol	60 gr.	86

This table is based on the number and percentage of worms actually removed by certain doses of the drug, and not on the number of "cures" or percentage of persons cured by the drug.

The efficiency of thymol and beta-naphthol is greater in larger doses, but those larger doses are regarded as being beyond the limits of safety.

The Kind of Purge.—Carbon tetrachloride and beta-naphthol are laxative in themselves and do not require an adjuvant. Castor oil is precluded in giving chenopodium or thymol because the toxicity of the drug is increased on account of increased solubility and absorption. Magnesium sulphate is recommended.

The Susceptibility of Children.—Children are more susceptible to the effects of these drugs and most of the serious and fatal cases attendant upon their use are in this class of patients, but this is particularly true of chenopodium and carbon tetrachlorid. In regulating the dosage it is prudent to use a somewhat smaller amount than would be calculated from Young's rule.

Treatment by Oil of Chenopodium.—A preliminary saline purge of magnesium sulphate, 30 gm., is given in 300 c.c. of water after the evening meal the night before treatment. This purge is not necessary, however, when the dose is given in divided form. The following morning food of any kind except a cup of coffee is interdicted. At 7 A. M. 1½ c.c. of oil of chenopodium is given in a hard gelatin capsule with a swallow of water. Soft capsule preparations are relatively insoluble and should not be used. At 9 A. M. a full saline purge is given with a full glass of water. After the patient's bowels have acted well he may have breakfast if he desires. Between the time of administration of the vermicide and the purge, the patient may feel more comfortable in a recumbent position, for there is usually some dizziness, deafness and vomiting. These symptoms, however, are prevented to a great extent by giving the evening purge and by making the evening meal as light as possible or even denying it entirely.

Special attention must be paid to inducing free purgation after chenopodium, for the serious cases are often those whose bowels are confined after the administration of the drug. It is also prudent to remove the toxic drug along with the worms and not permit it to remain in the bowel after the vermicidal purpose has been accomplished. The time of the orderly or nurse may be economized by eliminating the preliminary purge from the treatment. In this case it is obligatory to give the drug in divided doses so as slightly to prolong its action, to obtain sufficient contact with the worms and thus gain the full vermicidal effects of the drug and avoid allowing too many worms to remain after the treatment.

A light supper is permitted the evening before treatment and at 7 A. M., on a fasting stomach, half the dose (0.75 c.c.) is given in a hard gelatin capsule. At 9 A. M. the other half (0.75 c.c.) is given. At 10:30 A. M. a saline purge is administered with a full glass of water. Breakfast is permitted after the bowels have acted well, but not before. Treatment should be repeated, if necessary, but never within from ten to fourteen days, for the drug is cumulative in its action.

This dose rarely gives any concern through severe toxic symptoms in adults. Whatever discomfort occurs usually disappears after the post-vermicidal purge. Whenever the dose is divided there is no good reason for giving the purge the night before treatment other than to prevent vomiting or dizziness, for the purge and the divided dose are reciprocal in effecting removal of worms. Even a small amount of food taken with the chenopodium greatly diminishes its vermicidal powers.

In spite of opinions to the contrary, the author is convinced by personal experience in tests carried out for the purpose of comparison that the administration of castor oil is associated with more toxic symptoms than magnesium sulphate when used as a purge, and should, therefore, not be used in treatment by chenopodium. Smillie believes that castor oil, by causing an abundant flow of bile, causes the solution and absorption of chenopodium in this secretion, thereby increasing its toxic action.

Children are peculiarly susceptible to the effects of chenopodium; in treating them, therefore, it is necessary to exercise care that too large a dose may not be given. One smaller than that calculated from Young's rule is advised. Experience has indicated that the following dosage is safest in the treatment of children:

Age in Years	*Dose in Cubic Centimeters*
4	0.2
6	0.3
8	0.4
10	0.6
12	0.7
13-14	0.8
15-16	1.0
17-18	1.25
19-20	1.5

A standardized pipet only should be employed in measuring doses, for drops from different sized pipets vary too much in size to warrant their use.

Emulsions of chenopodium prepared with acacia tend to separate and yield dangerous toxic doses; besides, chenopodium is not so active in emulsions as when it is free.

Chenopodium is a neurotoxin, its untoward effects are directed against the nervous system, namely, vomiting, dizziness, internal ear deafness, paresthesias, such as tingling of extremities, muscular incoördination and semicoma; these and albuminuria are more marked after large doses and dietary errors. The oil has only been used extensively the past few years and its pharmacology is very imperfectly known.

Cases of poisoning should be prevented as far as possible by free postvermicidal purgation. It is essential that the drug be removed by thorough irrigation, for in cases of poisoning purgation is difficult or impossible. Depression of circulation or collapse should be treated by stimulation with strychnin and digitalin, and by the application of warmth to the surface of the body. To prevent renal irritation hypotonic salt solution may be given by the Murphy drip.

Contra-indications to the Use of Chenopodium.—Being a neurotoxin, chenopodium is chiefly contra-indicated in nervous disease; it should not, however, be given to those suffering from chronic or acute dysentery or to pregnant women.

Treatment by Thymol.—This drug has been very extensively used in the treatment of the disease and many still prefer to use it. But it is not such an efficient drug as chenopodium within the limits of a safe dose nor is it so effective against the more resistant Ancylostoma duodenale or Ascaris.

Thymol should be administered in as finely divided a state as possible so as to insure close contact with the worms. It may be triturated and mixed with sodium bicarbonate or sugar of milk.

When given by the usual method a preliminary purge is taken the evening before. This should be of magnesium sulphate, not of castor oil, for the reasons advanced above. No evening meal is allowed. The next morning at 6 A. M., half the dose of thymol is administered and at 8 A. M. the other half. The postvermicidal purge is given at 11 A. M. It is important to interdict the use of greasy foods, milk, fats and alcohol during the course of the treatment.

The standard dosage recommended by Howard is:

Apparent Age	*Dose in Grains*
1 to 5	3 to 5
6 to 10	10 to 15
11 to 15	15 to 30
16 to 20	30 to 45
21 to 50	45 to 60
Over 50	30 to 45

The toxic symptoms encountered after thymol are muscular weakness, vertigo or giddiness, gastric and intestinal irritation, abdominal pain and vomiting, albuminuria, headache, tinnitus aurium and visual disturbances, cyanosis and collapse. These symptoms should be combated by free catharsis, and the bowels must be thoroughly emptied. Coffee may be freely given and, in cases of collapse, strychnin and other stimulants should be resorted to.

There are a number of persons regarded as being medically unfit for treatment with thymol. Many of these persons are suffering from malaria, anasarca, edema, chronic nephritis or cardiac disease or are very weak and infirm. While they are not regarded as safe risks for thymol, they have been successfully treated with chenopodium.

Treatment by Carbon Tetrachlorid.—A very efficient vermifuge has recently been introduced by Hall. This drug resembles chloroform in its chemical constitution and tests made by Smillie and Pessoa at the Instituto de Hygiene, São Paulo, Brazil, show it to have a higher vermicidal power than any other drug that has been used. It is receiving extensive use in tropical countries where severe hookworm disease exists, and upwards of 50,000 cases have been treated. The drug seems to have a specific action on Necator, the species found in the Southern States, but it is not so effective in removing males as female worms. Furthermore, it is *not* effective in removing Ascaris lumbricoides.

The drug is easy to administer, there being no symptoms other than some vertigo, and it is taken with less repugnance than chenopodium or thymol. No cathartic need be given for the drug possesses a laxative effect of its own.

The drug is still in the experimental stage and it must be recorded that several cases of severe toxic character have followed its use in what have been regarded as doses within safe limits and there have been five fatalities in children. From the chemical structure of the drug we should expect to find that it might cause hepatic necroses in the same manner that necroses follow the use of chloroform. And this is what has been found in dogs experimentally treated with carbon tetrachlorid. Necroses have been detected in the liver of one of the fatal cases in a child referred to above.

Three c.c. must be regarded as the maximum dose of the drug for adults. Pessoa believes that larger doses than 1.5 c.c. cannot be used with safety. Smillie and Pessoa have suggested the use of a combination of carbon tetrachlorid with oil of chenopodium or ascaridol, the active principle of chenopodium. In this way the combination would effectively narcotize hookworms and ascarides while the toxic powers of the drugs would be divided and partly spent on the liver (carbon tetrochlorid) and partly spent on the nervous system (chenopodium).

Treatment by Beta-naphthol.—This drug has been used in many places. Its adherents advise its use because it can be administered without taking the patients away from their work, because no bad effects follow its use, and because of its greater efficiency than other vermicides. In spite of unfavorable reports, the drug seems to find favor in many hands. But it is as dangerous a drug as any, and it is less efficient than either carbon tetrachlorid or chenopodium. In malarial localities or where there is fragility or instability of the erythrocyte from any cause, beta-naphthol is a dangerous drug to administer. It has been found dangerous also in certain localities where the malarial element could not be demonstrated as being present.

In using these vermicides it is a question of balancing one dangerous drug against another and of ascertaining the optimum dose which can be administered without bad effects, that is to say, the dose that will remove the most worms with the least likelihood of causing serious symptoms. We may dismiss beta-naphthol with the statement that it is not free from danger; it is not efficient against ascarides; it is only efficient against hookworms when administered in very large and unsafe doses and in these doses it is very likely to cause blood destruction producing symptoms like blackwater fever.

Symptomatic Treatment.—Very anemic patients require prolonged periods of rest and careful dieting. The heart is seriously damaged in the very worst cases. Transfusion has been carried out on certain cases in whom the anemia was extreme and the blood-forming organs exhausted. Iron in the form of freshly prepared Blaud's pills should be given, but it will be found that the administration of iron does not markedly accelerate the rate of increase in hemoglobin in the blood. The erythrocytes respond more rapidly than the hemoglobin to rest and dietary treatment. It is difficult to introduce into the dietary of some Orientals sufficiently nutritious and varied food, for they are accustomed to rice and are limited to chicken, goat's flesh and milk. These articles should be supplied in abundance when the patients are ready for a solid diet. Most cases of hookworm infection merely require removal of the worms.

Rate of Recovery after Treatment.—The rate of recovery after treatment depends on the number of worms harbored, the length of time and severity of the infection and the amount of exhaustion of the blood-forming organs.

Patients whose hemoglobins are no lower than 70 per cent return promptly to normal at the rate of about 1.5 points per diem. When the hemoglobin is lower, a proportionately longer time is required to raise the blood to normal. In the more severe cases when the hemoglobin registers below 20 per cent and has been at this figure for long periods, it is not to be expected that the blood picture can be brought back to normal. The rate of regeneration in severe cases is no more than 0.5 points per diem, although in young persons, not quite exhausted, the rate of 1.0 points per diem has been observed. When the hemoglobin is 40 to 50 per cent on admission, it was only 61 per cent on discharge and fifty-three days were required to bring it up to this point.

Patients whose anemia has been severe, and from whom many hookworms have been obtained after treatment, should be watched carefully for evidence of re-infection. These very severe cases often occur in persons who possess little or no resistance to the disease, and, whereas the ordinary person acquires only a dozen or more worms in a year, these susceptible persons appear to acquire four or five times as many in the same time.

Mass Treatment.—In the Orient and in fact every region of high endemicity where the worm index or average number of hookworms per person is 100 or 200 or more, and where practically every person above six years of age is infected, there is urgent need of mass treatment to get rid of the tremendous burden of infection borne by the people.

By mass treatment is meant the administration of vermicide, to large or small bodies of people—all the inhabitants of a community, village, district or neighborhood; all the inmates of a plantation, institution, hospital, or any other group of persons living on and polluting and infesting more or less the soil of one area. This treatment is carried out within a few days and without previous microscopic examination of the stools of each and every person. But the index of infection is ascertained previously by examining a representative sample of the population preferably by worm count.

Mines and Estates.—Immigration and quarantine stations should be utilized in ridding all classes of persons, both expatriates as well as repatriates, from infection. Regular inspection of estate coolies and mine operatives should be carried out and treatment given whenever required. All new arrivals to estates or mines should go through a treatment station and receive thorough treatment before being thrown with other workers. No one should be permitted to go underground until free from infection.

Prophylaxis.—The existence and spread of hookworm infection is due entirely to such defective sanitation as permits the exposure of hookworm infected feces on the soil where the embryos of the worm have access to the naked skin of the people frequenting the polluted and infected spots.

A rational prophylaxis in this disease is easily conceived, and consists in providing suitable places for the disposal of dejecta and at the same time treating all the people who are infected by means of vermicides.

We now possess statistics which reveal the effectiveness of the latrine in reducing the amount of infection by preventing reinfection after treatment. Hackett carried out in Brazil a very thorough campaign against hookworm infection and, in one of the districts treated by him, a resurvey was made by Smillie on the lines carried out by the Uncinariasis Commission to the Orient, namely, by means of an actual count of the worms harbored by the people and not by a percentage of those whose stools contained ova. Three years after the campaign it was found that, in the small group of inhabitants who had received no treatment, and who had not used latrines, the average number of hookworms carried (the worm index) was 324. In the group of people who had been treated and had used latrines the worm index was only 2.2. In one group that had received treatment but had used latrines for only part of the time the worm index was 24. In still another group which had received treatment but had never used latrines the index was 31. This is probably the best demonstration extant of the efficacy of the method of combining treatment with soil sanitation. In this campaign chenopodium was the drug employed, usually in doses of 2 c.c. to adults. Many persons were treated to a cure by the intensive method and, at the close of the campaign, latrines had been installed in 80 per cent of the homes. It was then found that the actual percentage of persons still infected as disclosed by microscopic examination of feces was just as high as before the treatments were begun. This discloses the futility of depending on microscopic tests of ova in attempting to evaluate the efficiency of sanitary measures against this disease. Actual enumeration of worms is necessary, for in the campaign the worm burden was reduced from 324 to 2.2.

Installation of Latrines.—The essential problem in hookworm control consists in the installation of latrines; the expulsion of the hookworms harbored by the population; and the prevention of soil pollution.

Practically there are many difficulties on the administrative and economic sides of the problem, and there is an educational and disciplinary phase of the question of fundamental importance requiring prolonged and careful treatment.

It is usually expedient to begin a campaign in a locality by a combination of intensive treatment, educational propaganda and the installation of latrines. This may be modified by making a survey of an area and selecting from the different districts those which show the greatest amount of disease and treating them first. Wherever it is possible the installation of latrines should precede or accompany the work of medication so that the treated persons will not suffer reinfection from the soil polluted and infested by those not yet under treatment. Treatment should be intensive, that is to say, all the persons in the community should be treated. This is done by first making a census of them and insisting on each taking the medication. In many places it will be possible to institute mass treatment of entire communities, and thus rapidly get rid of soil infestation.

The type of latrines will depend on local, social, esonomic, soil and topographic conditions. Any method of disposal of dejecta is satisfactory which will avoid pollution of the surface soil accessible to bare feet, and not favor the breeding of flies nor pollute the drinking water supply. Neither should the system jeopardize the health of the service attendants.

The Earth Pit.—The earth pit is a simple type, and to be recommended in sparsely settled communities, on plantations, and construction work in rural districts. It is not suitable where soil water reaches near the surface, nor on flood plains, nor where rock lies less than ten feet from the surface.

The Bucket Latrine.—This type is useful out of doors or indoors where a well-organized conservancy or scavenger service can be maintained, as on construction works, in mines and in oriental towns. The excreta should be buried three feet below the surface, placed in large septic tanks or incinerated.

Concrete Vault Latrine.—This is built in two compartments and used alternately so that time is given for destruction of hookworm embryos during putrefaction.

Septic Tank and Privy.—The effluents of septic tanks have not yet been subjected to thorough investigation as to the viability of hookworm embryos, but it is generally believed that, when properly operated, destruction of the embryos is effected.

Incineration.—Incineration is a method having the advantage of destroying thoroughly all waste matter where there is a possibility of polluting the drinking water supply. It requires very careful supervision and stoking.

Water Borne Sewage.—This type is expensive and at times economically impractical; it is the system which should be used whenever possible. Latrines should be placed where the people will use them—not too far from barracks; and they should be kept as clean as possible. On plantations small pit latrines should be placed right among the trees to prevent pollution of the soil.

An educational program must be carried out in all those communities in which age-old and time-honored customs have required the people to pollute the rivers, streams, fields and groves.

Among primitive people illustrated lectures must be given in their vernacular. Hemoglobin estimation of infected persons and a demonstration of expelled worms are useful in arousing an interest in the gravity of the infection and in the necessity of taking steps against it.

Employers of labor on plantations should be shown the economic unfitness of their infected workers and be induced to carry out a campaign on their estates.

The disease is of so grave an aspect in some tropical lands that some widespread social agency should be utilized or created to bring about an amelioration of the condition of those severely infected persons whose physical condition is oftentimes extremely pitiable. The tremendous physical and economic handicap from which millions of these people are suffering needs urgent attention.

Infected miners should only be permitted to work on the surface. A system of disposal or conservancy should be installed underground and given careful supervision. When mines cannot be disinfected, ventilation and drying will tend to limit the development of hookworm larvæ.

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THE INTOXICATIONS

CHAPTER XXXVIII

CHRONIC DRUG INTOXICATIONS AND "ADDICTION"

Ernest S. Bishop

Terminology.—In order to simplify discussion of these subjects the writer is forced to a certain amount of generalization and the use of a nomenclature which has been so popularized in lay press and some pseudomedical discussions as to give it a connotation which, in the light of modern medical knowledge, is indefinite and misleading.

One of the words is "addiction," whose use among the laity has now become so common and widely applied as to be found in almost every popular magazine of lay fiction or discussion and used in the most absurd connections.

The writer, therefore, wishes to state that, if the word "addiction" appears in this discussion, it applies solely to changed physiologic processes and their clinical manifestations, and is not to be confused with such terms as "habit" or "vice" or "mental craving."

The attempt of the author is to clarify the clinical consideration of these subjects on a basis of physiologic or pathologic action and reaction so that the practitioner of medicine will have a basis of fundamental clinical fact around which he can group whatever incidental manifestations may appear in any given case occurring in his practice of bedside medicine.

Classification.—In their physiologic or pathologic machinery and clinical manifestation, the drugs most commonly met with in the chronic intoxications and addiction group themselves under three general classes:

1. Drugs which stimulate nerve, or glandular, or other function.
2. Drugs which depress nerve, or glandular, or other function.
3. Drugs which inhibit nerve, or glandular, or other function.

Exhaustion of nerve, or glandular, or other function may follow continued overstimulation, or may come to exist as a result of continued depression or inhibition.

It is the opinion of the author after many years of observation and study that it is most essential and clinically practical that these various drugs, differing so widely in their primary physiologic and other action, should be dissociated from description or discussion under any common designation such as "habit-forming," and considered either individually or in such groups as may have some common attribute in their effect upon the physiologic mechanism and machinery of the human body.

The author has found it most practical to approach them and the effects of their continued administration from the standpoint of immediate effect and subsequent reaction in terms of body function.

This is particularly important for the reason that many of the clinical manifestations commonly or popularly attributed are not *per se* the direct result of the action of these drugs, but are the result of disturbances in body function, either due to these drugs or to extraneous circumstances which should be studied out and taken into account by the competent physician in each individual case.

For instance, where psychologic or psychiatric manifestations exist (or may be thought to exist) in any given case, they should not be considered casually as customary or intrinsic concomitants, but rather analyzed as to origin and cause and effect in terms of the history of their development and all the circumstances of their appearance and manifestations in each individual case. The reason for this is that except in a few of the drugs of the first group (the nerve or glandular or functional stimulants and excitants), there are no primary or immediate mental effects directly due to the administration of these drugs in a majority of cases.

1. DRUGS WHICH STIMULATE NERVE, OR GLANDULAR, OR OTHER FUNCTION

In Group 1, as to immediate effect, are to be placed such drugs as cocain, cannabis indica, and, in many cases, alcohol. Alcohol, however, owing to some of its physiologic properties, cannot be invariably grouped in all cases under this class.

In overdosage or non-therapeutic indication, the drugs of this group reacting to produce immediate stimulation may be called, in continued administration, the drugs of indulgence.

Their abuse is often associated with either morbid curiosity or some inherent psychologic defect. They are stimulants whose overuse is followed by a reaction of physiologic depression, and it is to meet this reaction of physiologic depression that succeeding doses of these drugs are often self-administered. They are the drugs periodically or occasionally overindulged in by some individuals for the purpose of securing a periodic or temporary "jag" or "spree." They present an entirely different problem therapeutically in the treatment of their chronic intoxication than do the drugs of the second or depressant group, and those of the third or inhibiting group.

It is in this group that psychologic or psychiatric manifestations most commonly present themselves for consideration, and in which there is to be found most often a psychologic or psychiatric inherent or fundamental basis for overadministration or continued indulgence. It is also in this group that are to be most commonly found the end results of mental or moral or physical degeneration or deterioration. They are the drugs responsible for the loss of self-control which leads to some of the crimes so luridly exploited in the sensational press from time to time as being committed by so-called "dope fiends."

It is a matter of common recognition among informed persons and in reliable statements and literature that the crimes of violence associated either directly or incidentally with the use of drugs are practically confined to individuals under the effect of the "drugs of stimulation or indulgence" referred to in Group 1, such as cocain, hashish, or alcohol. It must be remembered that in these drugs of Group 1, as well as in all other drugs or toxic substances, individual susceptibility or resistance varies within wide limits, and that no dogmatic statements of amount or of reaction are invariably applicable.

In the therapeutics of chronic intoxication from the drugs of this group, it should be kept in mind that the bodies of those affected are in a condition of more or less constantly alternating overstimulation and its reaction of depression or exhaustion, and are therefore in a condition of metabolic unbalance which adds to the toxic effect of the drugs themselves a very serious burden of intestinal or autotoxemia and autotoxicosis, and contributes greatly to the production of malnutrition, anemia and other accompanying manifestations.

It is a matter for serious consideration in each case and for clinical estimation that these elements, resulting more from the functional depressions following overstimulation than from the stimulation itself, should be recognized and met.

The chief and immediate clinical consideration in the therapeutics of these cases of chronic intoxication with the drugs of Group 1 (the drugs of stimulation, sensation and indulgence) is the meeting of the depression or exhaustion of function which comes as a reaction to overstimulation, and the elimination of the autogenous and other toxins resulting from that depression and exhaustion.

In these drugs of Group 1 there is no constantly present or pathogenic set of physical "withdrawal symptoms," such as are invariably found in and are clinically diagnostic of the condition of true "addiction," or addiction-disease, and confined to the drugs of the inhibiting or opiate group.

The clinical symptomatology and therapeutic indications, therefore, in the handling of chronic intoxications from Group 1, or such stimulating drugs as cocain and alcohol, are the ordinary symptomatology and indications for therapeutics in any overstimulated state followed by depression and exhaustion of function with its consequent retention of autogenous toxins.

There has been found as yet no clinical or research evidence of the existence or development in these states of a peculiar mechanism of definite and invariable pathologic significance such as adds another and distinguishing factor to the true addiction or addiction-disease condition developed by the body in the case of prolonged administration of inhibiting or opiate drugs.

The development of a peculiar mechanism of protection and set of clinical symptoms sharply divides the clinical and therapeutic problems of continued administration of opiates from the clinical and therapeutic problems met as a result of prolonged administration of all other drugs.

This is supported by the present available preponderance and prospective development and outcome of reliable serologic and other laboratory experiment and clinical experience and study. This matter of the peculiar and distinguishing elements and factors presented by a group of physical reactions and symptoms found only in the inhibitory or opiate group will be discussed more fully in a later section of this article.

The absence of any particular physical phenomena (accompanied by invariable physical suffering), attendant upon the withdrawal or discontinuance of cocain, hashish, alcohol and the other drugs of stimulation and indulgence, makes their discontinuance, either voluntary or enforced, a far simpler clinical and therapeutic problem than is to be met in Group 3, or even in Group 2. It also makes the ultimate prognosis far more uncertain and subsequent resumption of administration of these drugs of Group 1 through self-administration more likely.

As is stated before, they are drugs of stimulation, sensation and indulgence, and their removal is not accompanied by the agonizing physical phenomena which are the invariable concomitants of deficient or lack of administration of the inhibiting or opiate group, in cases of developed addiction disease.

The individuals concerned under the classification of Group 1 are, therefore, without memory of severe physical suffering upon removal of their drug, and moreover, as I have also stated, are more liable to be of the types of the deliberate or irresponsible indulger in abnormal stimulation or sensation, and affected by the fortuitous circumstances of association and environment.

The clinical and therapeutic problems of the treatment of this class of patients, therefore, reduce themselves to the common-sense fundamental of applying the ordinary remedies and practices in the care of the overstimulated and subsequently exhausted or depressed, and whatever intercurrent conditions of nerve or other organic or functional change may have taken place as a result of the prolonged alternation of overstimulation and subsequent depression or exhaustion of function with its manufacture of autogenous toxins.

It is probably upon the head of these autogenous toxins that the blame must ultimately be placed for many of the organic changes in liver, kidneys, circulatory organs, nerves, etc., heretofore casually attributed to the direct action of or indulgence in alcohol itself and the other drugs of this group.

In this class of patients also there frequently enters the question of psychologic or psychiatric consideration, and the problems of mental training, education, reëducation, etc. These of course must be handled as they appear in the individual case, and by the most practical means available to the personal position and financial status of the friends or relatives of the patient.

The immediate care of the patient in this class depends of course upon whether he is received for treatment in a stage of overstimulation or in the stage of subsequent reaction with functional depression or exhaustion.

Every physician in private or institutional practice is familiar with such problems. It is wise in so far as possible to avoid medication which may depress or inhibit function. Such drugs, aside from any psychologic influence they may have upon the patient, only add to the end results of the either present or succeeding depression or exhaustion state.

In a stage of extreme and violent excitement, it may be necessary both for the protection of the patient himself and for those about him to have emergency resort to hypnotics or sedatives. The drugs of the inhibiting or opiate group should be administered to this class of patients only under most rare and emergency circumstances. Aside from the danger of subsequent recollection of relief and quietude and support which the patient might receive from their administration leading to unwarranted future self-medication, it must be remembered that they inhibit function, and the prime and fundamental consideration to be constantly kept in mind is the elimination of toxins and the restoration of function.

The drugs of the hyoscyamus group (such as hyoscin) are to be given with the utmost caution. Their administration may be beneficial and indicated in a given case, but it is to be remembered that individuals in a state of depressed or exhausted function are very variable in their personal reactions to all drugs, and that, moreover, the pharmaceutic preparations of the drugs of the hyoscyamus group are not always uniform in preparation and potency and that in these states there may be a cumulative effect or absorption with serious if not fatal results.

Whatever drug may be given to meet the emergency or hypnotic necessities of what may be called emergency medication in the stimulation stages or manifestation of those suffering from continued indulgence in these drugs of Group 1, it must always be remembered that there is to come a succeeding state or phase or reaction of depression or exhaustion of function, and that the earlier preparations are made for the meeting of this reaction, the quicker and better will success attend the efforts of the physician.

It is my opinion, from careful and continued personal observation of many cases in Bellevue Hospital and elsewhere, that the so-called "alcoholic wet-brain" is more often a result of the overadministration of depressing or inhibiting medication during the period of primary stimulation than it is of the alcohol per se.

Having learned this through my own personal observation, the above statement is no more of a reflection upon others of the medical profession than it is upon myself and my earlier therapeutic efforts.

It was undoubtedly some similar experiences which led Livingston to the advocacy of the routine use of ergot in alcoholic and postalcoholic cases, and other depression and exhaustion states. It has undoubted clinical and therapeutic value, and should be kept in mind along with strychnin and the drugs of the digitalis group, and other supportive medications and measures, to be applied with therapeutic judgment in these cases.

It is especially important that such supportive measures should be employed and begun early in cases which show violent manifestations and which may call for temporary emergency administration of some hypnotic or nerve sedative. As I said before, the preparations of the inhibiting or opiate group should only be used in times of rarest emergency.

Strychnin is a most valuable adjunct in the treatment of these cases. Its early and continuous employment, in selective doses to meet the transient and changing reactions and requirements of these cases, is not only of value in the prevention or amelioration of the toxic and starvation or exhaustion nerve complications which may exist or arise later, but it stimulates peristalsis and aids in competent evacuation of whatever toxic material may be eliminated into the intestinal tract.

In the severe cases of chronic intoxication or even some acute intoxication by the drugs of this first class of stimulation and indulgence, a symptom or phenomenon which may occur and give rise to sudden emergency is atony of the stomach with its well-known serious concomitants and possibilities. The stomach and its tone and area should, therefore, be carefully and constantly watched. Gastric lavage with hot saline and bicarbonate is, therefore, an emergency measure of greatest therapeutic importance, and should be kept up until the stomach is cleared of its contents and regains approximately its normal size, tone and motility.

During my connection with the alcoholic wards of Bellevue Hospital, I devised a special nasal stomach tube of particular consistency and resiliency and shape or form of introducing end. These tubes were made by Tiemann and Company and could be gotten in various sizes so as to accommodate the different nostrils. In adopting this route and method of gastric lavage in these cases, I obviated much of the struggle and necessity for mouth gags in washing the stomach of a violent or excitable individual. I mention this because it is my opinion that every possible expenditure of nervous or physical energy should be saved to these people to have in reserve against the stage of exhaustion or depression succeeding overstimulation and activity, either resulting from the effect of the drug of their indulgence, from the as yet uneliminated intestinal or other autogenous toxin accumulating in their periods of functional depression, or from their own violent exertions.

A rapid acting and in my experience valuable cardiac and circulatory medication is furnished by spartein as recommended by Jennings of Paris and Pettey of this country. This circulatory supporter has wider recognition and use in Europe than it has received in this country. In my experience the reason for its more efficacious results in European practice is to be found in their employment of larger doses, ranging for the adult from ½ to 2 gr., instead of the far smaller doses stated in our own materia medicas. I myself have seen little or no result from the administration of these smaller doses, and have come to adopt the European estimate and measures for therapeutic results.

It has been in my experience a striking phenomenon that in even the excited stages of such manifestations, as some of the types of delirium tremens, strychnin in full doses accompanied by rapid acting support to circulation and at times gastric or colonic lavage will have a better sedative and even hypnotic action than the employment of some of the more commonly used sedatives and hypnotics. This procedure is, moreover, not followed by a reaction of functional depression.

If it should seem advisable or necessary to use or continue medication of sedative or hypnotic type, such as the bromids, chloral, and some of the coal-tar products, it is well to reënforce them and to rob them, so far as possible, of their effects of functional depression by the coincident administration of drugs which furnish circulatory, nerve and peristaltic support.

As to the administration during treatment of the drugs of chronic intoxication, classed under Group 1 as the drugs of stimulation, sensation and indulgence, it is well to be guided by the occurrence and manifestation of the after-effects of depression and exhaustion consequent upon their deprivation or withdrawal.

The earliest possible and practical complete withdrawal or deprivation is always indicated.

It must be borne in mind in their administration and in the estimation of their dosage during treatment that they are being administered to an individual whose body has become physiologically tolerant to their action, and that they should be given in dosage to meet required therapeutic effect in the overcoming of depression or exhaustion (until this indication is successfully handled through other medication), and that the ordinary materia medica dosage for the average person has no significance as applied to these cases. The size of the dose needed in each particular case must be determined by experience.

In many cases immediate and absolute deprivation and withdrawal is therapeutically feasible. The clinician must exercise his own judgment as to the reactions of the patient and the extent of underlying functional exhaustion, depression and toxemia.

As to elimination, there need be and should be no consideration of any set procedure of catharsis. In fact, the competent clinician can far better exercise his own judgment than be guided by any preconceived impressions or advice. Cholagogues and secretory stimulants are indicated, and I have come to use saline cathartics less and less, except as indicated by the need for an occasional copious, watery evacuation which may assist in relieving renal or circulatory overburden, or else in cases where I believe a relief of liver and other congestion and content of toxin storage is indicated as soon as possible. Catharsis should never be carried to the point of exhausting purgation or of producing an irritative mucous colitis. By such ill-advised catharsis producing exhaustion or mucous colitis, the object of real and competent elimination is often aborted and defeated.

True elimination is not to be measured in terms of quantity or frequency of bowel evacuation. It is to be measured in terms of restoration of circulatory, glandular and renal function to competency, as indicated by the usual clinical signs and manifestations.

In the drugs of this group (the drugs of stimulation, sensation or indulgence, with secondary depression), as in the drugs of Group 2 (those which primarily depress nerve or glandular or other function), the phenomenon of tolerance of increasing dosage to a point ordinarily lethal for the unaccustomed individual is probably explainable by the rapidly stimulant or diffusible action of these substances, and by the benumbing or failure of response by the body, due to the constantly recurring depression of nerve or gland or other function, by their reaction and by the accumulation of autogenous toxins.

In the light of present knowledge and information this seems to be the explanation of most practical credence, and separates the drugs of these two groups from the chronic intoxications of Group 3: the true pathologic addictions or "addiction-diseases," to whose mechanism seems to be added another factor which will be discussed later.

2. DRUGS WHICH DEPRESS NERVE OR GLANDULAR OR OTHER FUNCTION

In the chronic intoxications with the drugs of the second group are to be found some of the coal-tar analgesics such as phenacetin, and the hypnotics like veronal, chloral, etc. (and sometimes alcohol in some of its effects and uses).

These are not drugs of indulgence or sensation or stimulation or addiction. The beginning and continuing of their administration to the point of chronic intoxication is usually, if not almost invariably, a result of the attempted meeting of some therapeutic indication of real or occasionally fancied existence, such as headache, sleeplessness, nervousness, etc.

Only too often such clinical manifestations are themselves only symptoms of some condition of physical or functional depression or exhaustion. So that the relief of pain or other symptom from continued individual dosage of these coal-tar and other depressants may be only temporary, and the added functional depression of the drug taken for relief adds to or aggravates the machinery of causation and the manifestations of the symptomatology primarily existing which led to the original medication with these analgesic or hypnotic drugs—which are usually functional depressants in their effects.

So that the patient who continually administers the coal-tar analgesic or hypnotic is almost invariably adding to the burden of preëxisting physical depression and intensifying and perpetuating the original symptomatology for whose relief the coal-tar depressant was primarily sought.

In some cases I have known this process to continue so long as to convert an originally transient nervous or other affection into a subacute or chronic condition or lesion.

Fundamentally, therefore, the therapeutics of this class must take into account the underlying cause for which relief was primarily sought, and must correct this condition as an essential part of the treatment of these individuals for their chronic intoxication.

It is a mistake for these individuals to make too much of an open issue of the mere fact of their constant medication with these drugs. It has been my experience that most of them have strong recollection or present experience of the physical or nervous or other condition for which they sought relief in this medication. Furthermore careful clinical examination and historical analysis of the development of the patient's present condition will show the existence of some actual lesion or condition of pathology or function or psychology which is a very real and material clinical fact, and upon which the whole history of and cause for the medication is based.

To the patient this history and past experience is the most important element for consideration, and it furnishes a basis for distrust if the physician does not seriously regard and analyze and correct it; and without the element of confidence and trust in the physician's clinical and diagnostic ability, and assurance of relief of the underlying cause for medication, but little will be accomplished in the care of these cases.

My own experience has been that with but few exceptions it was wiser to place but little emphasis upon the medication administered and that, as soon as I had discovered and corrected the original cause for self-medication, the continued use of whatever drug of this group was in question was gradually and voluntarily abandoned.

Many of these cases show either an anemia or an apparent anemia which easily corrects itself once the circulatory and functional tone is restored, and whenever toxins of metabolic origin from functional depression are eliminated and intercurrent conditions corrected.

In other words, the therapeutics of this class of chronic intoxications resolves itself into the symptomatic treatment of the individual; and the mere fact of continued dosage with one or another of the drugs of this second group becomes purely incidental and self-eliminating under rational therapeutics and kindly attention and care.

3. DRUGS WHICH INHIBIT NERVE OR GLANDULAR OR OTHER FUNCTION

In the chronic intoxications with the drugs of Group 3 a physical element is introduced which gives them significance of intrinsic and paramount importance for clinical and therapeutic consideration, and which is not present in the drugs of either Group 1 or Group 2 so far as has been yet demonstrated by reliable clinical and laboratory research and study. This element apparently arises from the power which these drugs possess of inhibiting or blocking function, an entirely different mechanism from the mere reactions of primary depression following overstimulation or the direct action of depression, to which may be traced the clinical phenomena in Groups 1 and 2.

The complete and ultimate determination of the physical mechanism and pathology arising from this power of inhibiting function which is possessed by and characteristic of this group of drugs (and most remarkably demonstrated in the case of opium and its derivatives) is still a matter of much controversy. Since most of the clinical and laboratory research work and studies upon the drugs of this group have been made in connection with the derivatives of opium, it will render the present discussion more simplified if it is carried on in terms of this universally known and recognized substance. And since, so far as their pathological addiction or addiction-disease-forming qualities and manifestations and reactions are concerned, the various preparations of or from this drug (opium) are practically interchangeable, and the important studies and researches have been made upon the alkaloid morphin, reference to this group in this discussion as regards clinical observations and experimental findings will be to some extent in terms of morphin.

It will be borne in mind, however, by the reader that whatever is stated of morphin, applies equally, with certain unimportant physiologic differences in immediate effect and dosage, to all other derivatives and preparations of opium, such as codein, heroin, the tinctures and gum opium itself—with the one exception of apomorphin.

In opening discussion of the invariable phenomena, symptomatology and probable pathology of the condition of chronic intoxication with the drugs of the inhibiting or opiate group, the drugs which give rise to the formation of true physical addiction or addiction-disease, or, as it may some day come to be called, physical dependence, or "opiate dependence disease," it is well to select as an introductory example a type of case of this disease from which all incidental or concomitant manifestations of individual mental or moral, environmental, non-physical and non-pathologic extrinsic manifestations are automatically and unquestionably excluded.

Such example, in which the clinical and pathologic picture is cleared, is to be found in the well-known and often recorded instances of opiate addiction-disease with all its typical physical and pathologic manifestations and reactions existing at birth in infants born of opiate-addicted mothers.

That this opiate addiction-disease with its pathologic phenomena and reactions and clinical manifestations had its existence before birth and developed while the infant was still within the uterus of the mother, there can now be no scientific question or controversial discussion.

Practically all of the reliable scientific literature on the subject records and recognizes that the manifestations and phenomena develop unmistakably before the infant has had any postnatal association or contact with the mother. This explodes the popularly current fallacy that infant addiction is acquired through opiate content in the mother's milk.

The writer has record of personal observation of these cases of prenatally addicted infants, supported by the case histories and literature of many other observers and authorities.

As a rule such infants are born apparently perfectly healthy and normal in every way, unless birth happens during a time of insufficient opiate supply to the addicted mother, hence deprivation of supply to the unborn child, in which case the infant displays at birth the typical signs of physical body need for the opiate commensurate and identical in character with those exhibited by the mother at the time of the birth of the child.

If, as is usually the case, the mother is adequately supplied with the opiate of her addiction at the time of the birth of the child, the infant is born apparently normal and healthy, and develops and manifests the typical clinical "withdrawal" or "abstinence" symptomatology some hours later.

Unless supplied with opiate medication, either through the mother's milk or by other administration, it seems to be the consensus of reliable opinion that these infants usually die, after passing through the clinical symptomatology of opiate deprivation pathognomonic of this condition in the adult. The therapeutics of prenatally developed addiction-disease as seen in the newborn infant will be discussed later.

SYMPTOMATOLOGY OF OPIATE NEED OR DEPENDENCE

The pathognomonic manifestations or clinical symptoms of addiction to or physical dependence upon the drugs of the inhibiting or opiate group are now to be found in any standard textbook on the subject.

To quote from an article by the author,[1] this pathognomonic symptomatology may be described as follows:

"After addiction is once established, failure to administer the drug causes a chain of definite symptoms, varying in priority of onset, in sequence and in relative violence of manifestation in different cases. In a general way, they may be said to begin with a vague uneasiness and restlessness and sense of depression; followed by yawning, sneezing, excessive mucous secretion, sweating, nausea, uncontrolled vomiting and purging, twitching and jerking to violent jactitation, intense muscular cramps and pains, abdominal distress, marked cardiac and circulatory insufficiency and irregularity, pulse going from extremes of slowness to extremes of rapidity, with loss of tone, facies drawn and haggard, pallor deepening to grayness, exhaustion, collapse and, in some cases, death."

This pathognomonic symptom-complex peculiar to deprivation of or sufficient reduction in amount of the drug of addiction in cases of chronic intoxication, resulting from sufficiently long continued administration of the drugs of Group 3, is disclosed by study of the literature and by the process of elimination of all manifestations not constantly present in all cases under observation afflicted with this disease.

This symptom-complex must, therefore, be taken as the clinical picture of the fundamental indications for therapeutics and for consideration in the determination of the essential pathology in this condition. In other words, the mechanism which produces this symptom-complex is opiate addiction.

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[1] "Narcotic Addiction—A Systemic Disease Condition," Journ. Am. Med. Ass.. Feb. 8, 1913.

The recognition of this fact furnishes for the practitioner of medicine a solid basis for therapeutic measures which can be supplied in no other way. Any other symptomatology occurring in a case is extrinsic or complicating and must be accounted for upon the basis of some other explanation than the manifestations of opiate addiction *per se,* and must be so treated.

The failure to recognize this fact is responsible for a vast amount of misconception of these cases and also contributes to the explanation of the large percentage of failures in the application of routine methods, and special or "specific" "treatments."

The application of this fundamental principle is generally recognized and axiomatic in all other clinical conditions. In no clinical condition is its application more important than in the therapeutics of opiate addiction. This is especially true because in such a large proportion of these cases the primary and continued administration of opiate was in itself a therapeutic measure instituted for some other medical or surgical condition which may still persist and upon which the condition of opiate addiction is superimposed, sometimes to the extent of masking the continued manifestations or effects of the original disorder. The essential difference between this class of cases in Group 3 (the inhibiting or opiate group) and the gases of Group 2 (the depressant group) lies in the fact that, while the immediate and transient effects of the drugs of Group 3 are functionally inhibiting, they give organic support, while the drugs of Group 2 are depressing in their primary and continued reactions. The application of this will be discussed more fully later.

This explains the fact that a large proportion of the opiate-addicted maintain a physical robustness sometimes extending over many years of a long and useful life, during which the presence of their addiction is entirely unsuspected, while those chronically intoxicated with the drugs of Groups 1 and 2 early and almost invariably display both physical and mental depression and deterioration. The opiate-addicted who show marked mental or physical deterioration are those who began their opiate medication as a result of morbid curiosity, aroused through such mediums as sensational lay publicity; the influence of evil association upon the adolescent or inherently defective; or the deliberate working upon the same types of mentality by the agents of the illicit smuggling and peddling traffic which has developed in the last few years. An added factor of physical and, in some cases, mental trauma is to be found in the repeated undergoing of drastic and therapeutically unsuccessful efforts toward the relief or arrest of the mechanism of opiate addiction. This will be recognized by every experienced practitioner as equally true of other medical or surgical ailments, and has marked the history of the progress towards understanding and competent handling of practically all of the subacute or chronic disease conditions.

It is necessary, therefore, carefully to evaluate clinically all manifestations discovered in the histories of these cases, and to differentiate between the manifestations of addiction-disease itself, and intercurrent or complicating manifestations presented by each individual clinical picture. It is the rapidly growing conviction, as expressed by the most reliable authorities, that all intercurrent or complicating conditions should be searched out and relieved before the final stage of treatment—that of withdrawal of the opiate itself—is attempted. This conclusion is based not only upon the effects of withdrawal upon the intercurrent or complicating conditions, but also upon the fact that intercurrent conditions or unscientific management are responsible for the frequent failure at the final stage of treatment—the withdrawal of the opiate itself—and for many so-called "relapses."

Reliable studies of the blood and laboratory experiments upon opiate-addicted animals have very generally tended to confirm the earlier hypotheses based on clinical studies to the effect that the continued administration of opium and its derivatives, to the point of established addiction or physical dependence, sets up within the body of any red-blooded animal a mechanism of protection through the production of some antidotal toxic substance analogous to the mechanism of protection in conditions of blood immunity, anaphylaxis, etc.; and that it is this mechanism of protection and the arrest of its activity which constitutes the real foundation for the above-described pathognomonic symptom-complex, and the real problem to be considered in therapeutic effort.

In other words, it is of basic importance that the clinician in his treatment of these cases of opiate addiction-disease (or opiate dependence disease) should constantly bear in mind that, once addiction has been fully established as a constant and active mechanism in the patient's physiologic processes, the subsequent administration of the drug of addiction is for the purpose of meeting or counteracting the symptomatology and pathology of the pathognomonic mechanism. It is in many places an unfortunately persisting fallacy that sensuous or pleasurable sensation or deliberate indulgence play a part or are present as inherent factors in the opiate medication of addiction-disease, or that there is a psychologic impulse arising from alleged "appetite" or mental "craving" or desire for "enjoyment."

There is no fallacy or misconception which does more to obstruct and impair the therapeutic judgment and procedure of the clinician than the one just referred to. In retrospection, it formed in the writer's own early experience the greatest block to recognition of clinical fact and intelligent and successful therapeutic procedure.

The meeting of the pathognomonic symptomatology above referred to forms the ONLY rational basis for determination of opiate medication and dosage in the treatment of the opiate addicted.

Some of the incompetent generalizations and statements as to the dosage indicated for or required by the opiate-addicted, which have gained a certain amount of dissemination and credence, have worked great harm and have been serious obstacles in the true appreciation of the therapeutic problems of this condition among both the medical profession and the laity.

To show the practical futility of any estimation on the basis of the ordinary pharmacopeial or materia medica dosage of these drugs, as estimated for therapeutic effect upon those who are not addicted or physically dependent upon them, it is only necessary to read casually the literature of clinical authority upon this subject of opiate addiction. As Dr. E. H. Williams states: "There is a very general misconception as to the amount of opiate that is actually necessary to sustain the normal balance in cases of addiction," and "for practical physicians know that, whereas one individual will get along comfortably on one grain of morphin daily, his neighbor may require ten or twelve times that amount daily during the same period." In discussing the misconception prevalent in some quarters that the body of the opiate-addicted individual is only capable of utilizing "a certain definite quantity of morphin, and any amount taken in excess of this quantity is purely superfluous," Williams states that this must be the conception of such people as "some cloistered laboratory worker, who has had very little practical experience with human opiate users," and that it cannot be "the conception of any practical clinician who has ever come closely in contact with opiate drug addiction."

Williams further states that "as in the case of a person whose physical body need to meet the pathognomonic symptomatology is one grain per day, a sudden decrease will cause the exhibition of marked withdrawal symptoms invariably," so also if "a corresponding reduction is made in the case of a person who is taking ten times this amount he will show withdrawal symptoms just as inevitably as the person taking the smaller amount." He adds, "It is not a mental condition but an actual physical one, which has been demonstrated repeatedly, and may be demonstrated at any time."

Similar statements are to be found in my own writings and those of most competent clinical observers upon this subject.

These observations are indisputably supported by the fact that, in the administration of morphin to a person addicted and displaying the pathognomonic symptom-complex of physical body need above referred to, the "withdrawal" or "abstinence" symptoms are relieved and disappear exactly in ratio to the dosage administered and in reverse sequence to that in which they made their appearance.

It is beyond argument, therefore, that the dosage of opiate administered reacts physically and physiologically and is used by the body to meet in practically mathematical certainty of measure in each individual case some physical mechanism directly responsible for the production of the pathognomonic symptom-complex or physical "withdrawal" signs. *And this is the basic fact of opiate-addiction.*

Furthermore, the phenomena above cited absolutely detach for study and treatment the conditions resulting from the chronic intoxications by the drugs of Group 3 (the inhibiting or opiate group), as contrasted with the conditions resulting from the use of drugs of Groups 1 and 2 (the stimulating and the depressant groups).

It would be unnecessary to discuss any concurrent or incidental mental manifestations in connection with Group 3, if it were not for the fact that misconception of the nature of these conditions, of the chronic intoxications typified by opiate addiction-disease and its physical mechanism, had not been until recent years of clinical and scientific investigation, discussed rather widely upon a basis of previous scientific misconception and misinterpretation. Even in his early experience with such cases as came to the alcoholic and prison wards of Bellevue Hospital, the writer was surprised to find practically none of the euphoria and the dream states and other manifestations which he had been led to believe attended the administration of opiate drugs to the opiate-addicted.

The writer finally came to see that the supposed "euphoria" was not a direct action of the drug, but was the ordinary everyday sensation of relaxation and relief attendant upon the cessation of suffering. It is, furthermore, the author's observation that the "hallucinations" or "delirium" or "suicidal manias," etc., referred to in many places, are not a result of opiate-addiction itself, but are the result of prolonged suffering (mental and physical) to the point of desperation and physical and functional exhaustion, anxiety and fear, too often the result of the manner in which they have been handled. They are ordinary and typical "exhaustion psychoses," well known to any competent and experienced clinician or alienist. They are most frequently observed in times of "physical opiate need."

In the production of incidental or intercurrent mental manifestations, the coincident administration in some cases of drugs of Group 1 and occasionally of Group 2 may of course enter. An apparently misinterpreted self-realization of delusions and hallucinations of this type is described in De Quincey's *Confessions of an English Opium Eater.* De Quincey and the myriad of more or less able writers who have followed him, and have taken their text from his descriptions, have apparently failed to realize that De Quincey took his opiate in the form of laudanum and in sufficient quantities of that preparation to give him no inconsiderable daily alcohol ingestion. So that his hallucinations are more probably explained by alcohol than by opium, and, furthermore, are clinically typical of the effects of alcohol overadministration.

This same clinical deduction is to be drawn from careful observation upon the individual who takes cocain in addition to opiate. Such individuals belong, however, to a class of people who do not commonly come under the care of the medical practitioner outside of custodial institutions. They are not typical of the average case of opiate addiction, and are practically never seen in the average case of opiate addiction under conditions of rational management. As is stated above, the explanation for their appearance in any given case is to be looked for in the action of overstimulation or depression from some other drug than opium, or in the ordinary reactions to exhaustion, autotoxemia, suffering, worry and fear, or other commonly recognized and commonsense explanations of identical manifestations in the individual who is not opiate-addicted. This recital of the mechanism of their origin points to the obvious therapeutic measures for their prevention or relief.

The American pioneer clinician in the study of opiate addiction, Doctor George E. Pettey, pointed out years ago that the essential characteristic of opiates which reacted in the development of what he called "narcotic drug diseases" resided in their power to inhibit function. He attributed to this inhibiting power the locking-up by the body and progressive tolerance for opium and its alkaloids, and to this same inhibition in many cases an accumulation of toxins of intestinal and autogenous origin. Upon this as a basis, Pettey contributed the first extensive clinical studies towards the rational treatment of this disease. It is unfortunate that his real clinical work was lost sight of in the absurd reduction, by others, of his observations to the form and status of a formulated routine plan of treatment which came to be known as "The Pettey Treatment"—something which Pettey himself, as he told the writer, had never intended, and rarely followed in his own clinical work.

He did not, however, conceive that this inhibiting of function and consequent retention of opiate or its products might result in a separate specific pathognomonic mechanism of defense by the body and the production of definite antidotal toxins demanding, in themselves and by their continued manufacture, the neutralization or opposition by opiate medication, as elaborated and correlated with clinical facts by the author of this chapter in the *Journal of the American Medical Association.*[2]

The application of the power of inhibiting function and consequent accumulation of opiate or its products, reacting in the production of a specific antidotal protective mechanism and biochemical substance requiring opiate medication for its control, was later adopted by Dercum and Pettey and others as the essential pathology of opiate addiction-disease, and this appears to be substantiated by reliable laboratory experiment and research.

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[2] "Narcotic Drug Addiction—A Systemic Disease Condition," Feb. 8, 1913.

It is very significant that clinical study, laboratory experiment and research has, however, failed to produce any evidence pointing towards the existence of a similar mechanism in chronic intoxications from drugs which do not inhibit function, such as the drugs of Groups 1 and 2.

It becomes, then, of primary importance in the treatment of the opiate-addicted that the manifestations and extent of inhibition of function be made the subject of careful clinical consideration and estimation, and that all factors directly causing or contributing to this inhibition be removed or minimized. It should be unnecessary to repeat that fear, worry, and suffering, etc., are vastly important concomitant contributors in many cases.

As to the inhibition of function caused by the administration of opiate itself, *it seems to be the fact that its duration is not in proportion to the size of the dose of opiate administered.* On the other hand, *the length of time over which the administration of opiate will hold in abeyance the "withdrawal signs"* or *pathognomonic symptom-complex above described, is,* within certain limits, *in mathematical ratio to the size of the dose administered,* and can be made very much longer than the period of primary inhibition immediately following the medication.

The practical application of these two now commonly recognized physical or physiologic phenomena is discussed in my paper before the Section of Pharmacology and Therapeutics of the American Medical Association in 1916 and printed in the transactions of that section—"The Rational Handling of the Narcotic Addict"— from which I quote as follows:

"Inhibition of function lies at the bottom of the formation of addiction mechanism. Inhibition of function is the chief obstacle to the well-being of the narcotic addict. The control of inhibition of function is of fundamental therapeutic importance in the care of the narcotic addict.

"The difference in clinical picture presented by different narcotic addicts is so strikingly apparent that it demands explanation. One addict is constipated, malnourished and loaded with the poisons of intestinal and auto-intoxication. He is in wretched organic and functional tone, showing poor reaction and poor resistance. Another addict is apparently healthy and normal and physically and mentally competent. I believe that the cause of the difference lies in the presence or comparative absence of inhibition of function.

"The extent to which inhibition of function is present seems also to exercise a strong influence upon the amount of drug required to hold in abeyance the suffering of narcotic drug need. In other words, the addict functionally inhibited requires more drug to maintain him in narcotic drug balance than he does uninhibited."

This quotation provides the practical application of the two principles of clinical or physical phenomena just stated: (1) that the period of inhibition following opiate medication in the addicted is not in ratio to the size of the dose administered; and (2), that the length of time over which a dose of opiate drug will maintain a patient free from the sufferings, incapacity and symptomatology of drug need, is within certain limits in mathematical ratio to the size of the dose administered.

In brief, with any given amount of daily medication necessary for the control of the withdrawal sufferings and symptomatology, in any individual case, at any given time, the fewer number of times in a day a dose of opiate drug is administered, the greater is the extent of competent metabolism present, the more adequate is the patient's elimination and nutrition and physical tone and function, the smaller amount of opiate drug or its products lies stored in inhibited or atonic cells and, hence, the smaller amount of antidotal substance is required to be manufactured and to be met by opiate medication.

So that in the care and treatment of the opiate-addicted it becomes an important principle of therapeutic procedure to administer the amounts of opiate drug, determined upon as being the patient's minimum amount of daily physical need at any given time, in large doses and at wide intervals. This is important for the securing and maintaining of physical tone and reaction irrespective of whatever other therapeutic procedures may be determined upon as clinically indicated in any given case. By the observance of this procedure the body of the addicted patient is restored to average in reaction and normal response to all medication administered or prescribed.

Following upon a period of observance of this principle it will be found that drastic eliminative medication is unnecessary and that the intestinal tract thereby escapes the transient or permanent trauma which is so often attendant upon the unduly drastic and often ill-timed cathartic medication of some of the routine "treatments" or "methods" so-called.

The observation of this principle also makes far safer and more effective the administration, when indicated, of other drugs, such as those of the hyoscyamus and belladonna group, and the dosage of them required for therapeutic effect much smaller and approximating those which react in therapeutic doses upon the healthy individual. It has the further advantage of aiding in the uncovering and correction of intercurrent or concomitant conditions which may be present and operate to interfere with or prevent the successful clinical discontinuance of opiate medication, or provide a basis for subsequent opiate medication which might reactivate the addiction-disease mechanism in a very few doses in the permanently sensitized body of the opiate-addict. Permanent, because it must be recognized that once the opiate tolerance and body dependence and pathognomonic symptom-complex have developed and become established, the mechanism which creates them is probably never lost but is only rendered inactive to remain as a latent or dormant body function, reactivated at any subsequent time by a very few doses of the substance which originally led to its development. It has been pointed out that in this phenomenon opiate addiction shows an analogy to certain of the anaphylactic mechanisms such as, for instance, that associated with poison ivy. Every patient should have this phenomenon of physical mechanism strongly impressed as such upon his understanding, and should be told that, in all future surgical or medical emergencies, his physician should be appraised of this situation.

As a practical prophylactic against subsequent reactivation of the arrested and dormant addiction mechanism, the information in the last previous paragraph will accomplish more than any amount of lectures on "will power" or other mental or moral dissertations. For the prevention of the physical facts of physical origin a knowledge of those facts is the most essential requisite.

The failure to recognize and generally disseminate knowledge of these physical facts is largely responsible for much of the failure in therapeutic administration and for the vogue of scientifically meaningless words and phrases which have gained currency and at times have dominated the consideration of this subject. An illustration of this is to be found in a phrase which has come to be used rather commonly as descriptive of a *supposed* stage in addiction therapeutics, and upon which emphasis has been laid and erroneous publicity created to the effect of distracting from scientific and clinical fact. The author refers to the phrase "after care" as designating a too commonly supposed essential stage in opiate addiction therapeutics. This phrase has been responsible for the physical and mental wreckage of many thousands of useful lives. If the activity of the essential pathologic mechanism of this condition has been completely arrested by competent therapeutics, there is no more reason for the coining of any such word as applied to this disease than there is for applying it to the ordinary convalescence from any other protracted ailment.

Years ago the author came to the conclusion (now unquestionably supported by clinically demonstrable facts and laboratory findings) that the manifestations, mental, nervous and physical, of the phase too often following upon withdrawal of opiate drug, were due to a low-grade persistence in the patient's body of the essential mechanism of addiction-disease itself, and were really "post-withdrawal" symptoms, continuing in low-grade form the more agonizing manifestations of the now commonly recognized "withdrawal symptoms" or pathognomonic opiate addiction symptom-complex, and were evidence of unsuccessful therapeusis in the stage of treatment known as "withdrawal."

As appears in other of the author's writings and elsewhere, the non-recognition of this fact is responsible for the utterly useless and misleading deductions from many of the statistics of so-called "cures," claimed to have been accomplished by some of the administrative and special routine institutional treatment and other experiments. The admittedly high percentage of so-called "relapses" is largely accounted for by actual failure of the therapeutic procedures employed and by the consequent persistence of the physical addiction mechanism producing "post-withdrawal" symptoms, with their attendant endocrine, circulatory and other functional imbalance.

It was the author's recognition of this fact, after continued failure upon other hypotheses, which led to his clinical analysis and study for explanation of these "post-withdrawal" symptoms, and his recognition of the practical therapeutic necessity of preventing their appearance, in so far as possible, by the institution of therapeutic procedure which eliminated the apparent mechanism of their production, before attempting final withdrawal of the opiate.

From the ordinary everyday experience of the clinical practitioner in the various diseases or conditions with which depression or inhibition of function is a common clinical factor and auto or other toxemia commonly observed, it should require no argument or discussion to point out the fact that these concomitants with their well-known manifestations and effects, are not to be overcome nor their stored-up products eliminated, and functional tone and balance and recuperative and reactive ability restored, in any such length of time or amount of attention as has been given by some of the so-called "methods" of treatment, hitherto advocated for the "withdrawal" of opiate drug. It is quite generally accepted that the amount of the autogenous biochemical product or "antidotal" substance, for the alleviation of whose toxic effect opiate is administered in these cases, is dependent upon the amount of opiate or its products present in the body at any given time; that the cells of the body have developed a sluggishness of response in the elimination of this opiate or its products, and that thereby is created a residue of activating material irrespective of the current intake of the drug of addiction.

It, therefore, becomes apparent that the "post-withdrawal" symptoms are probably due to a mechanism activated by this residue persisting in inhibited or atonic cells even after the elimination of the current intake of the drug of addiction.

On this hypothesis the author long ago came to lay as much, if not more, stress upon the preparation for withdrawal of non-reactive and complicated cases, as toward the accomplishment of "withdrawal" itself. It should be obvious to any practical and competent clinician that eliminative response and recuperative ability in an individual afflicted with any clinical condition is the paramount factor in successful recovery. And since the extent of residual opiate or other toxins is so largely an element in continuance of the "postwithdrawal" symptomatology of this disease after too hasty or unskillful withdrawal of the current intake, the removal of this residue before withdrawal of the opiate becomes a matter of the greatest importance.

I therefore worked out and instituted as fundamentally important in treatment, a "stage of preparation," which is now recognized and adopted generally by the modern and reliable authorities and writers on the subject of the opiate drug and allied diseases or chronic intoxications with inhibiting toxins.

The conduct of and duration of this stage cannot be predicated or arbitrarily stated in advance any more than can the management and reaction of the same or analogous inhibitory body processes in any other chronic disease condition. The principles of its management are the rational application of the reactions and clinical phenomena already stated in this article, combined with such supportive and eliminative treatment as are familiar to every competent physician and meet the requirement of the individual case at any given time, never forgetting that the sufferer from opiate addiction-disease is a disease-afflicted human being and that kindly and understanding treatment and encouragement will accomplish more than any arbitrary or forcible methods.

For elimination, the regulation of the interval of opiate administration is of paramount importance and assisting in this strychnin or some other peristaltic stimulator may be well used in dosage to meet the varying conditions of the inhibition state, plus the transient inhibiting action of the current intake of doses of opiate medication itself. Intestinal, eliminative, glandular, circulatory or other medication should be administered in non-irritative form and with recognition of the reactive elements as above outlined in these cases. There can be no formulated routine and there can be no set procedure.

The same statement applies with equal force to the management of the stage of treatment known as "withdrawal of the drug." There has been a very unfortunate tendency to discuss this stage as all-important in treatment and in terms of various so-called "methods," instead of in terms of physical body processes and symptomatology and reaction and the meeting of their therapeutic indications according to the judgment of the informed and competent clinician.

For example, we read and hear much of such terms as the "hyoscin treatment," the "belladonna treatment," the "gradual reduction treatment," and more recently the "ambulatory treatment," and the "institutional treatment," etc., etc. Each of these misleading phrases represents a dominant idea in some individual's or group of individuals' minds, focusing upon some incidental issue of detail in medication or management, and without scientific or clinical comprehension of the pathologic, clinical or other problems and therapeutic considerations involved in the treatment of addiction-disease and all other chronic conditions in the practice of medicine.

There is no competent therapeutic procedure which can be comprehensively designated by any of these terms.

I wish to emphasize this fact in order that the reader may clear his mind for the consideration of fundamental facts and rational therapeutics, and may regard the afflicted individual from whom he is "withdrawing" opiate medication as a sick person to be watched and studied as closely and clinical observations made as carefully and indications met as open-mindedly, as would be the case in the treatment of pneumonia, or cardiac, or any other disease in which the label of a routine medication or "method" or "treatment" would be met with jeers by an informed profession.

For example, although the preparations of the hyoscyamus group (best known in scopolamin or hyoscin) have undoubted value as useful medication at times in many cases, it is the writer's opinion and the growing consensus of all authorities that *they possess no specific qualities as curative of addiction-disease,* but are useful as indicated for their analgesic, antispasmodic, amnesic and other qualities in the hands of those familiar with their use. It might be said that their employment during the active withdrawal stage of treatment is analogous to the anesthetic employed by a surgeon during an operation, and is no more responsible for the physical events which take place during the period of amnesia or anesthesia than the anesthetic of the surgeon. The hypodermic administration of the alkaloids of this group is always preferable to the oral administration of any of their products, during the stage of active withdrawal in the treatment of opiate-addiction. The reason for this is that during this stage absorption from the intestinal tract is varying and uncertain, and the action and reaction of the drugs of the hyoscyamus group can, therefore, be far more competently controlled through administration in a manner which is not dependent upon uncertainties of intestinal or stomach absorption.

In regard to so-called "gradual reduction" procedures, or as to therapeutic procedure involving or including periodic reduction in the amount of opiate administered, the clinical manifestations and indications should be the guide, rather than any arbitrarily timed or predetermined reduction in amount. It has been found, by Sollier and others, that the clinical phenomena of opiate deprivation or of opiate body need are accompanied by changes in the blood practically identical with those accompanying infectious diseases. Clinically and pathologically unindicated reductions in amount, therefore, keep the body of the addicted patient who is being unskillfully or unscientifically "reduced" in a constant condition analogous to subacute infection with its wearing and wasting and exhaustion of the bodily processes and function.

In the stage of final withdrawal of the drug of opiate addiction, the practitioner of medicine should not be bound by any one "method" or "treatment" for withdrawal or deprivation of drug, but should keep his mind as open to all clinical and therapeutic possibilities as he would in the care of a patient suffering from any other disease.

As the author stated in his article "An Analysis of Narcotic Drug Addiction":[3]

"Success will attend the physician in exact ratio to his clinical ability, training, and experience and to his familiarity with the methods and remedies used to meet indications, and to his broad humanity and common-sense vision."

As a rule, the patient from whom opiate drug is being withdrawn, has undergone previous unsuccessful attempts by various "treatments" or "methods," and is perfectly familiar with their therapeutic procedures and their faults as applied to the physical actions and reactions of the inhibitory or opiate drug dependence or disease in his own case and personal experience.

Quite contrary to the statements made in some places, the author and other modern clinical students of this disease have been forced to the conclusion that these patients will gladly, and, if necessary, heroically, co-operate with the employment of any measures which have a rational therapeutic basis and which offer reasonable hope for the actual and complete arrest of the activity of the mechanism.

It is unfortunate that as shown in the report of the Narcotic Committee of the American Public Health Association[4] a questionnaire of the medical schools reveals so little clinical teaching in the past of this "withdrawal" and "postwithdrawal" symptomatology as a clinical disease entity.

The patient appreciates his affliction in terms of this pathognomonic symptom-complex, and the physician, to be successful, must observe and approach it therapeutically in the same terms.

It is the experience and opinion of the author that "gradual reduction" of opiate to the point of ultimate discontinuance can only be accomplished successfully by observance of the conditions (as above outlined) which enter into or affect the pseudophysiologic or pathologic body process by which the amount and extent of intake of inhibitory or opiate medication is regulated and determined, and that, without the constant observance of all of these conditions, failure of successful outcome is inevitable.

Some of these conditions, such as anxiety, worry and fear, have often been the result of forces beyond the control of the medical practitioner and rational therapeutics. Also, in some cases, it seems to be a physiologic impossibility to discontinue the final amount of opiate administered without having persisting circulatory, endocrine, and other imbalance and disability leading to the continuance of conditions which incapacitate the patients and may render them either chronic invalids, or lead to the development of other conditions of greater gravity than opiate addiction-disease itself.

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[3] N. Y. Med. Journ., Feb. 27, 1915.

[4] Am. Journ. Pub. Health, January, 1920.

In certain cases and types, this last observation is recognized by all authorities as applying to discontinuance of opiate medication by any method, including that which is generally known as "gradual reduction."

It is apparent, therefore, that while continued reduction of dosage to the point of ultimate discontinuance may be a procedure of election in some cases under favorable conditions, it is clinically and therapeutically contra-indicated in others. As frequently employed in a routine or irrational manner, the patient is brought to the point of ultimate discontinuance in a condition of exhaustion and prolonged strain and physical discomfort or suffering which renders the arrest of the addiction-disease mechanism itself and the early restoration to normality of body processes and function impossible.

An alternative procedure of election is that of more or less rapidly "withdrawing" opiate medication with the opiate dosage at whatever point may be found in the individual case to give the patient maximum functional and organic support and competency, maintaining such dosage until all other pathologic elements are removed, as discussed above in my references to the stage of preparation and observation. It is the author's opinion and experience, as well as the growing consensus of clinical and scientific observation, that wherever competent nursing is obtainable in surroundings where inhibiting, exhausting or depressing influences are eliminated, this is the plan of election in most cases. It should be stated, however, that the author has seen this plan fail in cases in which the more gradual "withdrawal" (or a combination of the two) subsequently succeeded.

It should be again emphasized that dogmatic assertion is as unscientific and as unpardonable in connection with this disease as it is in connection with any other condition in medicine and surgery.

It has been the author's experience that his best average results were obtained by making use of whatever remedial agent or physiologic reaction, secured from study and trial of all methods and procedures, was applicable clinically at any given time. As in any other disease condition, so in this, he succeeds best who is most familiar with all possible procedures and processes and wisest in their selection and application.

It is the author's experience that (when competently conducted without undue strain and suffering to the patient) the stage or step in treatment known as "withdrawal" of the drug should be accomplished in the shortest practical time commensurate with the reactive ability of the individual patient, and following the complete elimination of all toxic residues or other complications. Once this is accomplished, the pseudophysiologic or pathologic conditions and problems become simplified to the task of removing current intake without inhibition or exhaustion of function through undue suffering or other exhausting or inhibiting physiologic mechanism. Clinical observations upon the non-addicted and laboratory experiments upon laboratory animals, as well as both clinical and laboratory observations upon the functionally reactive addicted, show that the current intake of inhibiting or opiate toxins is disposed of without body residue in from three to five days. This fact has a bearing on the length of treatment.

In many cases (after the above functionally normal conditions have been consummated), with the skillful giving of anesthetic or analgesic medication, added to the continued maintaining of functional competency and eliminative tone, over a period of from three to five days, the body is relieved of the symptomatology caused by an active addiction-disease mechanism.

For the accomplishment of this purpose of analgesia or anesthesia or amnesia, the competent clinician must of course make his choice of the agencies with which he personally is most familiar and in whose handling he and his nurses are most skillful.

Representative of and perhaps most widely used (as well as most widely abused) of this class of remedial agents is hyoscin or scopolamin, illustrative of the action of the drugs of its group.

The general therapeutic use and the clinical applications of the drugs of this group have been (like the opiates themselves) too carelessly observed clinically.

As has been stated before in this chapter, these drugs are best given by hypodermic so that their action and reaction may be as carefully watched and controlled as the anesthetic administered during an operation. Stomach or intestinal absorption is too uncertain during this period to render advisable their oral administration. In the cellularly detoxicated and functionally reactive individual, the doses necessary for therapeutic action are but a fraction of those often given, and hence the dangers and manifestations of their toxic dosage are minimized or obviated. The unsuccessful results and deaths which have in the past given such medication an evil reputation are largely traceable to their being administered to an inhibited, toxic or exhausted individual in whom therapeutic reaction could only be secured by toxic dosage. This accounts for the cumulative toxic effects of various drugs and medications, frequently noted in the chronic infections, circulatory, glandular, and other states exhibiting inhibition, depression or exhaustion of function. It alone should be sufficient to prohibit or discredit the use of any routine procedure in these cases.

I have discussed the two broad principles of procedures most commonly known under various names and labels. I have also discussed the pseudophysiologic and therapeutic principles underlying each, and their application.

Practically all of the advertised nostrums or "remedies" or "special" or "specific" treatments are more or less clumsy attempts to capitalize and apply one or more of the various principles and reactions above discussed, and hence need not be particularly referred to in this chapter.

There remains one other form or procedure of opiate deprivation for which Erlenmeyer has been made to stand sponsor in the general literature of this subject. That is the sudden and absolute deprivation of all medication by forcible means. Except in some jails and custodial or penal institutions, such procedure is no longer regarded as worthy of clinical consideration in the discussion of this condition from a medical or scientific point of view. Aside from the deaths which have resulted and are commonly recorded in many places, the sufferings undergone by a patient in the stage of completely established addiction, under this process, are so great as to produce inhibition or exhaustion of function and to defeat the end in view, namely, the arrest of activity of the addiction-disease mechanism.

So that while it is occasionally possible and practical to apply this "method" before the addiction-disease processes have become fully established, as a therapeutic procedure, this manner of "drug withdrawal" need be given only casual mention in a scientific textbook. It not only produces (in completely developed cases of this condition) the terrific shock and trauma of suffering and exhaustion, but it fails to arrest the fundamental physical processes themselves, which may go on, as discussed above, for many months as "postwithdrawal" symptoms with their long protracted and often unendurable subacute manifestations of the original disease mechanism.

It should be remembered as an axiomatic fact that the mere act of administering opiate or inhibiting medication does not constitute addiction-disease, and that the mere fact of stopping this medication (or that it has been withheld for weeks or months) is no clinical or scientific evidence of the arrested activity of addiction-disease. This fact is demonstrable by both clinical and laboratory evidence, and should be constantly kept in mind by the physician, whether he be engaged in private practice or in institutional work.

There is probably no chronic condition of internal medicine whose activity and pathognomonic symptom-complex may be more completely arrestable in a greater percentage of cases, by the application of rational therapeutic principles under normal conditions of clinical treatment than inhibitory or opiate drug addiction. And for this is required merely the application of the ordinary therapeutic remedies and measures to the clinically demonstrable symptomatology and indications of this disease process.

The physician must, however, know, and his nurses be trained in and made familiar with:

1. The symptomatology, reactions and clinical measure of the physical need for opiate medication in the addicted.
2. The symptomatology and reactions of the pathognomonic symptom-complex expressing physical need for opiate medication.
3. The clinical estimation and recognition of the symptomatology of inhibited function and of autotoxemia of whatever origin.
4. The clinical estimation and recognition of coexisting and interacting organic or functional pathologic conditions.

Upon the understanding and recognition of these factors, which are matters of common and everyday application in all other conditions of medicine and surgery, depends the successful therapeutic outcome and prognosis of the treatment of the chronic drug intoxications and addiction.

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CHAPTER XXXIX

ACCIDENTAL, SUICIDAL AND ABORTIFACIENT POISONING

JOSEPH C. DOANE

INTRODUCTION

Acute poisoning results when a single massive dose of a harmful drug gains entrance into the body. This dose may be very minute in actual quantity but may be termed massive in comparison to the usual lethal dose of the drug in question. It seems reasonable to the writer to describe under this heading also poisonings which result when two or more larger or smaller doses of a powerful drug gain entrance into the body with but short intervals of time intervening between them. It is evident that tolerance to any drug does not enter as a factor in acute poisonings since the body tissues have not been subjected to the effects of small doses taken over any period of time. Occasionally, however, grave symptoms are most unexpectedly absent when what is usually a lethal dose of the drug is taken, or the reverse may be observed and the patient suffer a fatal toxicosis when only a fraction of the ordinarily fatal dose gains entrance to the blood-stream. These occurrences may be explained by the existence of either an unusual natural tolerance or a decided individual idiosyncrasy towards the poisonous agent. For these reasons a definite and unchanging minimal fatal dosage cannot be stated for most drugs.

The ingestion of a drug in solution usually brings forth a much more prompt and serious systemic response than when the same substance is swallowed in solid form. When the stomach is empty, absorption of the poison is accelerated and the toxicosis accordingly more severe; when the toxic agent is swallowed with food or shortly after its consumption, absorption is retarded, the reaction less severe and recovery more likely. The nature of the drug, especially as regards an irritating or nauseating effect on the stomach resulting in early gastric rejection, often favorably influences the outcome of the case.

Usually gaseous poisons which gain entrance to the blood-stream through the respiratory tract are very prompt in their action. Finally, each case of poisoning is a law unto itself and no routine empirical or mechanical treatment is as effective as a rational therapeutic system based upon a thorough understanding of physical and chemical properties, physiological actions and metabolism of the substance responsible for the toxicosis.

BICHLORID OF MERCURY

(*Corrosive Sublimate, Mercuric Chlorid*)

Occurrence.—Mercuric chlorid is the most common cause of acute mercurial poisoning of a serious nature. The fact that of all the toxic chemical agents bichlorid tablets are most apt to be found in the household collection of medicines, as well as the knowledge possessed by many lay people through the medium of the daily press that bichlorid is frequently used as an agent of self-destruction, both serve to increase the incidence of accidental and intentional poisoning by this drug. Strange as it may seem, the popularity of aspirin as a self-prescribed remedy serves to increase purely accidental ingestion of corrosive sublimate, for very frequently the unfortunate person arises in the night and mistakes the shape and size of a tablet of the latter for the former drug. The son of a physician of the writer's acquaintance recently lost his life through this preventable mistake. As will later be described under the heading of abortefacient poisonings, not infrequently the use of solutions of bichlorid of mercury as a contraceptive douche or the insertion of a mercury tablet in the vagina for this purpose has often resulted disastrously for the woman thus seeking to avoid conception. Rarely in the irrigation of wounds with bichlorid solution, a mercury toxemia results but, unless large abscess cavities exist with walls which absorb this drug rapidly, serious harm is not done.

Absorption, Metabolism and Excretion.—Mercury combines with the body proteins very promptly, forming a toxic albuminate of mercury which was formerly supposed to be inert and therefore harmless. Recent studies have shown that the compound is poisonous and should not be allowed to remain in the body for any length of time. Mercury as the bichlorid is absorbed readily from both unbroken skin and mucous membranes, although much more rapidly and completely from the latter. Mercury is absorbed through the gastro-intestinal tract, reaches the liver through the blood-stream as the albuminate, is excreted by the bile and is then reabsorbed by the intestines.

After absorption and entrance into the circulation, mercury disappears rapidly from the blood. It is taken up partly by the white blood-cells in a nucleic acid combination, but the largest portion of mercury is deposited in descending order in the kidneys, liver, spleen, bile and intestinal walls.

Here the same nucleic acid combination takes place and in this rather firmly bound state elimination is delayed. Traces of mercury have been detected in these organs from four to six months after administration. Blumenthal and Oppenheim believe that the fixation and distribution of mercury in liver tissue is lessened by the administration of potassium iodid.

Mercuric chlorid, according to Sollmann, is eliminated by all channels. Welander has shown that the walls of the colon and upper rectum play an important rôle in mercury elimination. It has long been proved that the gastric mucosa also is actively concerned in excreting mercury after toxic doses. Lambert and Patterson have reported the detection of this drug in the sweat. It is probable that the major portion of inorganic compounds find their way out of the body through the intestinal tract while the kidneys discharge the greater portion of organic mercury compounds. Buchtala insists that iodids delay the urinary excretion of mercury.

Pathology.—The pathologic changes induced by mercuric chlorid are those of a corrosive poison coupled with a more or less generalized systemic effect. The upper gastro-intestinal tract is corroded and ecchymotic if a strong solution has been swallowed. There is also an acute inflammation of the lining of the colon and stomach. The erosion of the stomach may be extensive and actual perforation has been seen. The belief has been expressed that the necrosis of the intestinal walls is due to the formation of thrombi in the capillaries with consequent occlusion of the blood supply. Pathologic changes of great interest are seen in the kidneys. Heineke, among other writers, believes that the kidney of bichlorid poisoning is peculiar to this condition. In this belief Kolmer and Lucke do not concur. The kidneys may be normal or much increased in size, dependent on the time which has elapsed since poisoning. The tubules show necrosis with attempts at regeneration of epithelium. The glomeruli show no inflammatory reaction but their loops are frequently occluded with conglutinated erythrocytes. The tubules may be filled with hyalin or granular casts and deposits of calcium salts are often observed in the necrotic cells. The liver shows fatty and parenchymatous changes. The kidney changes are probably not due to the actual contact with mercury during the process of elimination, but are a part of the general toxic tissue change as a result of being bathed with mercury-laden blood. Burmeister and McNally believe that the changes in the kidney depend largely on the size of the dose, while the liver pathology is largely determined by the duration of the intoxication.

Lethal Dose.—The lethal dose of mercuric chlorid is usually stated as being from 7.5 to 8 gr. (0.5 gm.); for children from 3 to 5 gr. (0.19 to 0.32 gm). J. B. McElroy reports the recovery of an adult female after the ingestion of 52.5 gr. (3.43 gm). The average minimal fatal dose is about 3 gr. (0.19 gm).

Symptoms.—The symptoms which arise subsequent to the toxic absorption of bichlorid vary greatly. They are dependent on the amount and concentration of the drug, the food content of the stomach and the physical state of the drug as to whether it was in solution or solid form. They range from mild irritation of the mucosa of the mouth, pharynx and esophagus with metallic taste in the mouth, nausea and diarrhea, to early prostration, the severest grade of mucous membrane destruction and death from uremia. The symptoms may be divided into local, general and, more specifically, into gastro-intestinal, circulatory and renal.

Local.—These symptoms result from the direct effect of mercuric chlorid on the mucous membranes of the mouth and pharynx. The tongue is white and shriveled, or, if a very concentrated solution has been taken, actual bleb formation is seen. The breath is fetid and the patient complains of an acrid metallic taste in the mouth. There is a sense of heat and choking in the throat.

Gastro-intestinal.—In addition to the local symptoms in the upper gastro-intestinal tract enumerated above, the patient complains of a cramp-like abdominal pain which is at first epigastric and later becomes diffuse. There is usually moderate abdominal distention and tenderness on palpation. Vomiting is frequently the first symptom and is usually prolonged and violent in nature. The emesis takes place usually within the first hour after the ingestion of the drug. The vomitus consists of food particles and frequently of blood-stained mucus. There is always some degree of gingivitis and usually marked salivation. Thirst is intense. Diarrhea is a constant symptom, the dejections often containing fresh blood. Edema of the glottis and jaundice are rarer symptoms.

Circulatory.—There are always some signs of shock due to the violent corrosive action of the drug upon the gastro-intestinal tract as well as to a vasomotor dilatation of the vessels in the splanchnic area and a consequent stagnation of blood in that location. The pulse is weak and rapid, the blood-pressure lowered, the temperature subnormal, the skin cold and moist and, in some instances, early fatal collapse takes place. This early depression frequently soon passes away as a result of supportive treatment.

Renal.—The kidneys are the seat of a necrotizing nephrosis (McElroy) in which the tubal epithelium becomes necrotic and calcium salts are deposited. The physician must realize that, unless a fatal issue results early from shock or some other unusual occurrence, the patient virtually lives or dies by his kidneys. When the oliguresis, albuminuria and casts are delayed in making their appearance, as is often the case, the physician too often relaxes his vigilance and his treatment, believing all is well when such is not the case. The reduction in urinary output may occur in the first forty-eight hours or there may be no alarming reduction in secretion of urine for from four to ten days after poisoning. Indeed the gastro-intestinal symptoms may have begun to subside before any abnormalities of kidney function are noted. The reduction in amount of urine may range from a moderate oliguresis to a most stubborn anuresis. McElroy and others report periods of complete anuresis ranging from five to eight days with subsequent recovery. The writer has seen two such cases. With the decrease in the amount of urine goes an increase in the urinary protein constituents. The blood urea mounts to 100, 200 or even 300 mg. per 100 mils and the uric acid content may be greatly increased. The blood creatinin mounts from less than 1 mg. to 10 or even 15 mg. per 100 mils of blood. The phenolsulphonephthalein output often quickly falls below the limit of safety, that is, 30 per cent concentration. Rosenbloom has shown that on about the eighth or tenth day the rising urea nitrogen content of the blood reaches its peak. Marked edema is usually conspicuous by its absence and convulsions seldom occur. In unfavorable cases the continued urinary suppression is followed after a longer or shorter time by nausea, muscular twitchings, hiccup, drowsiness, Cheyne-Stokes' breathing and coma. With the appearance of these ominous symptoms, dissolution is usually not long delayed.

Acidosis.—The lowering of the blood alkali reserve is a metabolic disturbance dependent on some change in ketone metabolism. Its exact cause is unknown but it is thought that this condition often antedates renal breakdown. The acidosis of a nephritis is not a ketosis. Acidosis clinically manifests itself by coma, intermittent dyspnea, the presence of acetone and diacetic acid in the urine and a low carbon dioxid tension in the alveolar air.

Diagnosis.—Statistical reports on special treatment used in bichlorid of mercury poisoning are frequently misleading because they often list cases as cured in which no mercury entered the body. The deserted woman often feigns an attempt at self-destruction to regain by pity a love which she has lost by infidelity. The recovery of mercury from the urine, feces or vomitus is infallible proof of poisoning. The appearance of the tongue or pharyngeal mucous membranes, the history and ensuing symptoms are usually diagnostically sufficient.

Prognosis.—One-half hour after poisoning by mercuric chlorid is the shortest time on record in which death has occurred. Death usually occurs within seven days. The majority of cases succumb in which more than the lethal dose of 8 gr. (0.5 gm.) has been taken and in which time for absorption has elapsed before attempts at removal took place. The outlook for recovery depends entirely on the size of the dose and the rapidity of its absorption. If the stomach is thoroughly emptied within one hour, recovery frequently ensues. If the drug has been taken in solution, absorption is hastened. If anuresis lasts longer than three days, the prognosis becomes proportionally less favorable, but recovery has taken place even after eight days of anuresis. Even in the absence of urinary suppression, death may result from acidosis.

Preventive Treatment.—The United States Pharmacopœia prescribes that the official tablet of mercuric chlorid containing 7.5 gr. (0.5 gm.) must be:

1. Angular in shape.
2. Stamped with the word, "Poison," with skull and crossbones.
3. Colored blue, preferably.

These requirements prevent some accidental poisonings. Some cities wisely forbid the sale of bichlorid of mercury to the laity. The regulation requiring the dispensing of bichlorid in angular or porcupine bottles not mistaken in the dark for containers of harmless drugs seems reasonable. The connecting of each tablet in the bottle with the rest by means of a thread or cord appears a wise measure. Instructions by physicians to the members of their clientele in regard to the danger of self-dosage and to the wisdom of looking at least casually at all objects which they entrust to their digestive apparatus might avoid serious trouble later on in many cases.

Immediate Treatment.—It is better to treat nine patients strenuously who have not swallowed mercuric chlorid than to waste one hour deciding whether the tenth person, who has, needs treatment.

Treatment must not be delayed for the appearance of symptoms nor, because the urinary output is sufficient at the time, must the need for prompt and continuous eliminative measures be underestimated. The following emergency treatment should be administered:

1. Give the patient at once the white of four eggs in one quart (1,000 mils.) of milk. If eggs are not available use milk alone or milk and flour mixed to the consistency of cream.

2. Remove the milk and egg mixture in one minute by siphonage through a stomach tube by introducing enough warm water to start the return flow. Remember for the sake of confirming the diagnosis to save a specimen of the washings for laboratory testing.

3. If nausea and retching persist, wash the stomach again in thirty minutes, using warm water. Repeat routinely twice a day.

4. Save the first urine voided to test for mercury and the first stool which the patient passes after the first day of poisoning has elapsed for the same reason.

Special Treatments.—At this juncture, the emergency treatment incident to the mechanical removal of the drug from the stomach having been given, the physician must adopt the plan of action which will be followed for the ensuing two to four weeks. He has the following from which to choose:

1. The alkaline-eliminative treatment of Lambert and Patterson.
2. The calcium sulphid treatment suggested by Haywood and Allen and later advocated for clinical use by Wilms and Holm.
3. The sodium phosphite treatment advised by Linhart and Carter (Carter's antidote).
4. The sodium hypophosphite treatment advised by Fantus and Rosenbloom if the phosphite is not to be procured.
5. A combination of the above dependent on the ease with which the special drugs required can be procured as well as the nursing and laboratory facilities and resident medical attendance available. Frequently this option will be the only feasible one to adopt.

A more detailed discussion of the merits of the above forms of treatment will be useful.

Options.—1. This routine appears to the writer to deserve first mention because it seems to have been as successful as any and also because of the fact that it requires no equipment either in drugs or attendants which the general practitioner will not find usually available.

a. When vomiting has ceased give an alkaline mixture which serves to combat acidosis as well as to dilute the toxins and in so doing to save the kidney as much as possible from damage. The following is recommended:

Potassium bitartrate	1 dram	(3.9 gm.)
Sugar	1 dram	(3.9 gm.)
Lactose	½ ounce	(15.5 gm.)
Lemon juice	1 ounce	(30.0 mils)
Water	16 ounces	(500.0 mils)

Give 8 ounces of this mixture every second hour, alternating with milk in the same quantity.

b. Give continuously day and night per rectum by the drip method potassium acetate solution, dram 1 (3.9 gm.) to a pint (500 mils) of water.

c. Flush the colon twice daily with sodium bicarbonate solution or warm water in large quantities (1 to 4 gallons) to wash out any accumulated mercury.

d. Wash the stomach twice a day with sodium bicarbonate solution, 5 per cent, or warm water.

e. Give a hot pack daily. This treatment should be continued for from one to three weeks, depending upon the amount of drug taken and the presence or absence of mercury in the specimen submitted to the laboratory for examination.

2. This treatment is based on the theory that a chemical reaction takes place between calcium sulphid and bichlorid of mercury to form an inert substance as expressed in the following equation:

$$\mathrm{Ca\,S + Hg\,Cl_2 = Ca\,Cl_2 + Hg\,S}$$

a. For every grain (0.064 gm.) of mercuric chlorid taken, 1 gr. (0.064 gm.) of fresh calcium sulphid in 1 ounce (30.0 mils) of sterile water is to be administered intravenously. Wilms cautions that great care must be exercised in securing a fresh solution of calcium sulphid, since deteriorated preparations are very toxic on account of the deleterious action of the calcium radical on nerve tissue. Hydrogen sulphid, which is an active poison, is also found in old solutions of this drug.

b. Fresh calcium sulphid, 1 gr. (0.064 gm.) to the ounce (30.0 mils) of water, is used as a medium for lavage.

c. Calcium sulphid is given by mouth in doses of from 2 to 5 gr. (0.13 to 0.32 gm.) every two hours until the signs of mercurialism have passed away.

d. Symptoms are met by the appropriate treatment as indicated.

In late cases coming under treatment the intravenous route had best be adopted. Wilms reports success in the early cases by giving the drug by mouth in doses of from 2 to 5 gr. (0.13 to 0.32 gm.). This may be continued until the odor of sulphuretted hydrogen is plainly perceptible on the patient's breath. Then the quantity may be diminished but the administration is continued until all toxic symptoms disappear. Calcium sulphid solutions for intravenous administration should be freshly boiled, cooled and filtered through paper and placed in tightly stoppered bottles.

3. Carter's antidote is founded on the conception that mercuric chlorid is reduced to mercurous chlorid (calomel) in the presence of sodium phosphite. This action seems to be enhanced by the addition of sodium acetate as in the following:

Sodium phosphite	10 gr. (0.65 gm.)
Sodium acetate	5 gr. (0.32 gm.)
Water	4 oz. (120 mils)

The above amount of sodium phosphite should be given for approximately every grain (0.64 gm.) of mercury taken. The above mixture is given by mouth every hour. Intravenous use is also possible.

4. The rationale for the use of the hypophosphite solution is not so easily explained. The reduction to the phosphite has been disproved by Fantus. The solution used is as follows:

Sodium hypophosphite	15 gr. (1.0 gm.)
Hydrogen peroxid	1½ dram (6.0 mils)
Water	2½ dram (10.0 mils)

If the amount of poison is known, ten times as much hypophosphite should be given. This solution diluted may be used as a gastric lavage.

The above combination is given by mouth every fourth or sixth hour for several days.

Comment.—The dictum of Sansum, that if 1/16 gr. (0.004 gm.) of mercury for every 2.2 lb. (kg.) of body weight has entered the body tissues no known treatment will save life, should serve to emphasize, if capable of proof, the importance of speedy mechanical removal of the drug and the folly of neglecting or delaying this procedure in the belief that chemical neutralization can be accomplished after the drug has been absorbed. When early recovery takes place it is not probable that any considerable quantity of drug has gained entrance into the general circulation. Proof is not wanting that in vitro calcium sulphid, sodium phosphite and sodium hypophosphite interact with mercuric chlorid to produce harmless compounds. The rapidity of absorption of the bichlorid when introduced into the empty stomach, and the difficulty and uncertainty of actually bringing other chemicals into contact with this drug when entrance into the portal circulation has taken place, must all be given consideration when treatment is being planned and a prognosis given. The greatest confidence can therefore only be placed in methods which remove or neutralize the drug before it is absorbed. In regard to Treatment 1 in our text, no effort should be spared to utilize all the available avenues of drug elimination. Sansum and others do not believe that free diuresis adds to the patient's chance of recovery; yet it must be granted that the administration of alkalis in an acidosis is therapeutically sound and that elimination in a toxemia is of first importance. This form of treatment is believed by the writer to be very useful to the average physician, particularly if no hospital facilities can be secured.

There is no question as to the test-tube efficiency of sodium phosphite in conjunction with the acetate in reducing mercuric chlorid. To Linhart, who suggested this treatment in 1913, and to Carter, who clinically developed the idea, should go the credit for any good arising from its use. In combination with the eliminative measures above-mentioned, this antidote may add to the success of treatment. The use of the hypophosphite of sodium in the hands of Fantus and others does not seem to have been an improvement on the phosphite.

In the chemical laboratory calcium sulphid in the presence of mercuric chlorid will give rise to mercuric sulphid and calcium chlorid, both of which are non-toxic bodies. If the problem after the ingestion of mercuric chlorid were of the same test-tube simplicity all would be well with the patient. Sappington and Hoff have carried out some very careful animal experiments with this drug and their results were in no way encouraging. Wilms, Hohn and others working with animals as well as with patients poisoned with the bichlorid report brilliant successes with this drug. Haskell and Courtney, on the other hand, conclude that little or no good can be accomplished by the use of this drug which cannot be accomplished by normal salt or some of the alkaline solutions. Sabbatini urges the use of the sulphur compounds, hydrogen sulphid or sodium thiosulphate solutions, such as gargles, enemata and hypodermic injections to relieve stomatitis, colitis and to prevent or delay absorption. Holm says, "I feel that in the sulphids we have an absolute control over the action of mercury within the system."

Sodium bicarbonate has been urged as a drug which is useful in mercuric chlorid poisoning. Fantus states that its antidotal action is due, not to a precipitation of mercury, but to an influence on the mercury-body proteid reaction. An excess of sodium bicarbonate is said to render mercuric chlorid less corrosive. A 5 per cent solution of sodium bicarbonate is useful as a lavage or it may be incorporated in the alkaline drink mentioned above or may be administered by bowel.

When dehydration is marked and edema is not present, Fischer's solution should be given intravenously. The diet should be poor in fat and proteins and rich in carbohydrates for at least four weeks.

The shock should be combated by the usual measures. An alkaline mouth wash is useful and routine mouth cleansing by a qualified dentist is beneficial.

Decapsulation of the kidney does not seem to have given favorable results. Some physicians contend that the kidney should be relieved of its capsule earlier and that the results of this procedure would be better if not left as a last resort.

Transfusion of blood has yet to prove itself a useful measure.

Anderson and Harrold have irrigated the lower bowel through a cecostomy wound in bichlorid poisoning. Too few instances of this procedure are available in the literature to enable one to judge fairly of its merits.

The writer believes that a treatment which combines the promising features of the above options, which does not with unquestioning faith trust chemical reactions, but which with zeal and intelligence eliminates, neutralizes, alkalinizes and above all actually removes the poison from the system before absorption will gain the best results.

PHENOL

(*Carbolic Acid*)

Occurrence.—Because of the frequent use of phenol as a household disinfectant and on account of the fact that the public is widely acquainted with its toxic action, accidental and suicidal poisonings from carbolic acid take place in this country with considerable frequency. In the United States phenol is second only to carbonic oxid as a cause of suicidal death.

McNally reports that in Chicago, from 1905 to 1917 inclusive, out of 1,396 suicidal poisonings other than from illuminating gas, 714 or 51.1 per cent used phenol for self-destruction. In Philadelphia, from 1910 to 1921, 362 or 63 per cent of 567 cases of self-destruction chose carbolic acid to terminate life. Deaths from illuminating gas are not included in the latter series.

The odor and even the taste of dilute phenol is not entirely dissimilar to the modern cheap whisky and as a result phenol has been taken in mistake for this beverage. In surgical practice the application of phenol to a large denuded area or even to the unbroken skin has proved harmful. In the early days of antisepsis the use of the Lister spray was responsible for not a few poisonings. Occupational poisoning also is not unimportant due to the extensive use of phenol in many industries.

Absorption, Metabolism and Excretion.—Phenol is rapidly absorbed from mucous membranes and, though more slowly, through the unbroken skin. In the intestinal canal absorption is at first rapid but later, probably due to interference with the local blood circulation, absorption is very much retarded.

Pelkan and Whipple have carefully studied by means of animal experiments the normal metabolism of endogenous phenol. They have shown that more than one-half of the volatile phenols which are very toxic are oxidized by the mucous membranes of the intestines, the body fluids and the liver. The remainder are conjugated in the liver with sulphuric or glycuronic acid and as phenyl sulphuric and phenyl glycuronic acid are rapidly eliminated by the kidneys.

As a result of the above experiments it may be assumed that exogenous phenol will be metabolized in like manner and that the liver plays an important rôle in conjugating that portion which is not oxidized. Pelkan and Whipple state that free phenol appears in the blood for about thirty minutes and that conjugated phenols reach their highest point during the first and second hours after ingestion.

Phenol is distributed generally to all body tissues. As has been mentioned above more than one-half of the phenol is rather promptly oxidized. The remainder is excreted largely by the urine as conjugated ethereal sulphates, phenol glycuronates, pyrocatechin, and hydrochinon. The two latter impart the smoky color to the urine.

Traces of phenol have been found in the sweat.

Pathology.—Since phenol precipitates protoplasm by changing the solubility of the cellular contents (Bastedo), one expects to find definite and widespread destruction of all mucous membranes which have come in contact with this agent in concentrated form. The tissues of the mouth, pharynx, esophagus and stomach are at first whitened and corroded. The mucous membrane of the stomach may present the appearance of having had the tips of the rugæ seared as with a hot iron while the intervening mucous membrane appears normal, having been "hardened and fixed" in situ. Again the stomach lining may present an angry red appearance with spots of erosion. Perforation of the stomach sometimes occurs. The characteristic odor of carbolic acid is frequently detected on opening the stomach and intestines. The blood is often dark in color and fluid, the lungs congested and the venous system engorged. The brain and its membranes usually show no change except occasional congestion. There are no other characteristic pathologic findings.

Fatal Dose.—Sollmann states that the lethal dose varies from 8.5 to 60 gm. by mouth although dangerous symptoms have occurred from much smaller doses. Death has been reported from the ingestion by an adult female of 1.5 gm. The average suicidal draught in this country is believed by Macht to be about 1 ounce. This writer states that, assuming the average weight of man is 70 kg., the lethal dose for the dog approaches that for man, that is, 0.5 mils per kg. of weight.

Symptoms.—*Local.*—The local symptoms are those which arise from the contact of mucous membranes with an energetic corrosive poison and are prompt in occurrence. If taken by mouth the mucous covering of the lips, cheeks, and pharynx is whitened and hardened. There may be whitened patches or blebs over the neck or upper chest where phenol has been spilled at the time of swallowing. The appearance of this carbolic burn is rather characteristic. The breath is heavy with the odor of phenol. The patient complains of intense thirst and great burning of the mouth and throat and dysphagia is present to a marked degree. Abdominal pain is cramplike and often of such severity as to cause the patient to double up with agony.

General.—General effects occur almost immediately. Dependent on the amount and concentration of drug taken as well as the contents of the stomach, the patient will exhibit early grave signs with drowsiness and speedy dissolution or the local symptoms will dominate the picture. Not infrequently the patient first exhibits fear or anxiety, mental depression, twitchings, weakness and convulsions. The blood-pressure is low, the heart action is depressed, the pulse slow and irregular, the vasomotor system is unstable, the skin being cold and moist. The pupils are contracted, the conjunctivæ being often insensible to the touch. The respiratory rate is slowed and as the prostration increases the temperature becomes subnormal. In fatal cases the patient lapses into unconsciousness, the respiration becomes more labored and death results from paralysis of the respiratory center. Isaacs states that in his series the cases which recovered did not remain unconscious longer than from five to seven hours. In extensive burns of the skin with carbolic acid, general symptoms occur as a result of a toxicosis from local absorption. Albuminuria, abdominal pain and bloody stools have been observed to occur following cutaneous absorption.

Urinary.—The urine is scanty, smoky in color, usually well loaded with albumin and casts. Hemoglobin or bile pigments may be present. Phenol cannot always be isolated from the urine. There is usually an absence of sulphates as is attested by the absence of precipitation with barium chlorid. This latter fact is of some diagnostic importance. At times when the kidney has received gross insult from phenol both microscopic and macroscopic blood is seen in the urine.

Diagnosis.—This is never difficult. The history, the white pellicle on the tongue with the characteristic odor of the breath, and the smoky urine with the absence of sulphates facilitate a correct solution. Circumstantial evidence will in many cases determine the diagnosis.

Prognosis.—The danger to life in phenol poisoning is not always commensurate with either the time which has elapsed since poisoning or the amount of drug taken, although these are very important factors in estimating the chances of recovery. If the stomach contained food the prognosis is very much brighter than would be the case were the opposite true. Coma may exist almost from the start and the patient never regain consciousness. Even in cases where there has been no collapse or marked escharotic action, depression of the heart and the center of respiration may ensue after some hours and may deepen into death. Acute nephritis not rarely develops and endangers life. Cicatricial contractions may ensue as a result of extensive eschars. Death within twenty-four hours is the rule in most fatal cases.

Preventive Treatment.—Care should be exercised in the use of phenol dressings on broken or even on unbroken skin. Particularly should phenol vaginal douches, bladder or abscess cavity irrigations be carefully considered as to the danger of toxic absorption. Carbolic solutions should be used with extreme care in the treatment of the newborn. An appeal to the press on a preventive medicine basis to omit graphic detailed descriptions of suicides by this drug would tend to lessen its use as an agent of self-destruction.

Local Treatment.—If phenol has been accidentally applied to the skin, prompt washing with an alcoholic solution is immediately efficacious. If carbolic acid has been taken by mouth, prompt washing of the oral cavity with alcohol will prevent burning and remove the adherent acid in solution. The action of alcohol is not a chemical neutralization but a solvent one, therefore, the alcoholic phenol solution must be expelled as soon as possible.

For speedy reference the systemic treatment of phenol poisoning may be outlined as follows:

1. Removal of poison from the stomach by lavage.
2. If no tube is available, produce emesis by requiring the patient to drink large quantities of warm water.

3. Use in order of efficacy and ease of availability as a lavage:
   - *a.* Warm water, 3 to 6 quarts.
   - *b.* Sodium bicarbonate solution, 5 per cent.
   - *c.* Glauber's salt (sodium sulphate) solution (concentrated).
   - *d.* Alcohol, 10 to 30 per cent.

4. Leave 2 to 3 ounces of 50 per cent magnesium sulphate solution in the stomach.

A more detailed mention of the rationale and the methods of carrying out these treatments seems justified.

Lavage with Warm Water.—The physician should place his first reliance on mechanically removing the phenol from the stomach. If concentrated phenol in large amount has been taken the stomach tube may do damage by favoring perforation of a corroded stomach wall. In spite of the mass of experimental evidence available in the literature relative to chemical neutralization or alteration to less toxic substances, in all types of poisoning the superiority of the actual removal of the offending drug over any and all methods needs no comment. In the absence of any of the special solutions mentioned above, warm water in large quantities is to be used. Lavage should be practiced even though an hour or more has elapsed since poisoning, for a fair percentage of the drug may remain for a considerable time unabsorbed by the stomach due to the vascular spasm produced by its irritant and corrosive action.

Lavage with Sodium Bicarbonate Solution.—Isaacs, 1922, reports that in his hands a 5 per cent solution of sodium bicarbonate has been most useful. He uses from 3 to 6 quarts of this solution in washing the stomach and leaves from 2 to 4 ounces of a 50 per cent magnesium sulphate solution in the stomach. This drug has the added advantage of being usually procurable from the household supplies. Isaacs believes that the bicarbonate of soda exerts its beneficial result by hastening elimination of phenol and by preventing kidney damage. He reports that the stay in the hospital of patients who are treated with sodium bicarbonate as a lavage and intravenously is shortened.

Lavage with Concentrated Sodium Sulphate Solution.—A concentrated solution of sodium sulphate or Glauber's salt should be placed next in order of importance as a lavage because of its efficiency and availability. The use of this drug in phenol poisoning was first suggested by Baumann in 1876. His belief as to its efficacy has led many others to attempt to confirm his findings. Cerna and Cafrawy working independently confirmed the value of this salt while Küster, Tauber and others doubt its usefulness. Macht in his admirable study prefers it to any other drug. Glauber's salt, however, is probably not a chemical antidote but possibly delays absorption and perhaps hastens elimination by producing purgation. Sollmann and Brown affirm that sodium sulphate is not a chemical antidote for phenol in acute poisoning. They show that a combination does not take place outside of the body either in neutral, weakly alkaline or weakly acid solutions. There is no evidence produced by these writers to prove that, when given intravenously, the effects of phenol are modified in any degree by solutions of Glauber's salts. As to the latter statement, all are not in accord, as some believe that with the sulphate a non-poisonous phenyl sulphonate is formed. It has been shown, however, that phenol combines with great ease with organic sulphur compounds when oxidation into sulphuric acid is taking place.

Sodium sulphate may be used intravenously in a 1 to 2 per cent sterile solution and from 500 to 1,000 mils injected.

Lavage with Alcohol.—Since the dramatic exhibition of Dr. S. D. Powell of New York City, in 1899, who washed his hands in pure carbolic acid and then likewise in alcohol without any apparent harm to himself, alcohol has been thought by some to be a true chemical antidote for phenol. Buchanan, Kelly, Phelps and others believed alcohol to be an antidote of great worth and efficiency. Clarke and Brown, in 1906, after making a careful search of the literature, were inclined to believe that alcohol as a lavage added nothing to the chance of recovery of the patients so treated as compared with other methods. Later these investigators, after experimental experience, concluded that alcohol as a lavage was an effective mode of treatment. Macht, 1914, strongly believed as a result of painstaking and exhaustive animal experiments that alcoholic solutions put into the stomach after phenol poisoning, by increasing the solubility of phenol, actually aggravate the damage already done. He states that in his researches alcohol which is ingested before the entrance of phenol into the system seems to affect favorably the patient's chances for recovery.

Clarke and Brown, 1906, concluded that alcohol is only effective when phenol is still in the stomach and that it does not display any marked superiority over water as a medium for lavage. They recommend immediate lavage with a 10 per cent alcohol solution followed by plain water in plenteous quantities.

Symptomatic Treatment.—Platt, in 1901, asserted that vinegar or dilute acetic acid was valuable in preventing burns by phenol when accidentally applied to the skin or mucous membranes. The writer has had no experience with their use.

For the gastric distress, orthoform or even morphia may be required. For the bleeding from the gastro-intestinal tract, calcium lactate or horse serum may be required.

Care should be exercised in passing the stomach tube when unconsciousness exists. At least one death is on record as a result of the tube having entered the trachea, the patient drowning from the lavage solution.

Artificial respiration may be useful in sudden depression of the respiratory center.

Due to the toxic effect of phenol on the heart, strychnin and atropin may be required. Intravenous administration of saline solution may be required to prevent circulatory collapse. Fischer's solution, which consists of sodium chlorid 1.4 per cent, sodium carbonate 0.37 per cent, and water 500 mils, is valuable for intravenous administration. Isaacs recommends a 2 per cent magnesium sulphate solution given by vein. External heat is often useful to combat shock.

Some observers advise against the use of oily remedies lest absorption be accelerated. Diluted raw whites of eggs and mucilaginous drinks in large amounts have been urged by some writers as useful.

The patient should be required to remain in bed until all signs of renal irritation have passed.

CYANID POISONING

(*Hydrocyanic Acid, HCN, Prussic Acid—Potassium Cyanid—Sodium Cyanid*)

Occurrence.—While accidental or suicidal poisoning with hydrocyanic acid or its cyanid derivatives is not as frequently observed as is the case with some of the other drugs mentioned in this chapter, yet the violent and ofttimes quickly fatal action of this drug or its salts justifies a description of the symptoms which result from its toxic action as well as mention of the chief indications for treatment.

In the series mentioned elsewhere (carbonic oxid poisoning) which consisted of the drug suicides in Philadelphia from 1910 to 1921 inclusive, only 43 or slightly less than 3 per cent of 1,429 victims of self-destruction chose cyanid. In homicidal poisonings about 0.5 per cent of recorded cases result from the use of prussic acid or its salts.

Small amounts of prussic acid are found in glucosidal form, such as amygdalin in apple seeds, peach kernels, apricots, cherries, plums, cherry laurel and the bark of the wild cherry. The oil of bitter almonds used as a flavoring extract contains four times as much prussic acid as does the official U. S. P. preparation of the same name. The defense in cases of suspected criminal poisonings has striven to prove the possibility of the prussic acid isolated from stomach contents being derived from the above fruits. Apricot, peach and cherry kernels consumed in large quantities by children have caused death.

Not a few fatalities have been reported as a result of inhaling the cyanid vapors of insecticides. The use of this gas as an insecticide is not as common in the United States as was formerly the case, although in the growth of citrous fruits in California and Florida these vapors are still used at times. In some cities the health authorities have used cyanid vapors as a means of fumigation. Lambert reports a fatal case of poisoning by this gas in a worker who was disinfecting a room. Führer states that clothing and fabrics absorb the gas readily and retain it for some time. He reports the poisoning of 100 soldiers who donned their clothing too soon after delousing with cyanid gas. Wilkes describes poisoning by hydrocyanic acid through a cut on the finger of a druggist handling this chemical. The cleaning of silverware by means of compounds containing hydrocyanic acid has resulted in poisonings which are fortunately not usually of a fatal nature.

Of historical interest is the turn of fate which caused the chemist, Scheele, to die as a result of the inhalation of the gases from hydrocyanic acid which he had discovered.

Absorption, Metabolism and Excretion.—While the rate of absorption from the stomach depends upon whether this organ contains food, yet this assimilation in every case is very rapid. Absorption takes place quickly through the respiratory tract when the vapors of this substance are inhaled. Prussic acid can be taken into the body through the broken skin and to a less degree when the epidermal layer is intact.

Prussic acid and its derivatives undergo very rapid decomposition in the body, a part combining with the molecular sulphur to form sulphocyanids. Another portion of this poison is excreted by the lungs unchanged, giving the characteristic odor to the breath. We do not know the fate of the remainder.

Bastedo states that in large doses the power of the cell protoplasm to utilize oxygen is destroyed so that the venous and arterial blood are of the same color and molecular asphyxia results. There is no adequate proof that any widespread combination with hemoglobin such as is seen in carbonic oxid poisoning takes place, although not a few writers refer to the creation of a cyanhemoglobin in poisoning with this drug.

The sulphocyanids are eliminated in the urine. The excretion of unchanged hydrocyanic acid by the respiratory apparatus has been mentioned above.

Pathology.—There are few characteristic pathologic findings in prussic acid poisoning. Upon abdominal incision the physician often detects the characteristic odor of bitter almonds. The blood is fluid from some interference with the action of the blood coagulative ferments. The color is often bright red, although in some instances the dark red color of venous blood is seen.

The eyes are often glistening and staring, the pupils dilated and the jaws set.

There is congestion of the viscera. The mucous membranes of the gastro-intestinal tract, especially if potassium cyanid has been ingested, are reddened and sometimes ecchymotic. In a case which was recently carefully studied by Lambert and his associates in which the patient survived for seventeen days after the inhalation of the gas of hydrocyanic acid, numerous small hemorrhages in the brain tissue were found. This was the case chiefly in the frontal and occipital regions, these changes being seen in both the cortical and medullary substance. The cerebellum seemed to have received the greatest injury for here marked cellular destruction was noted. This writer believes that so little is known of the possibilities of cerebral damage by hydrocyanic acid because life is rarely prolonged for a sufficient period of time for these lesions to develop.

Fatal Dose.—The lethal dose of the anhydrous acid (HCN) is about 1 gr. (0.06 gm.), of potassium cyanid (KCN) 3 to 5 gr. (0.2 to 0.3 gm.), of the dilute form of the acid about 37 gr. (2.5 mils). From 50 to 60 bitter almond seeds have given rise to a fatal poisoning. The largest dose reported from which recovery has taken place is 2.4 gr. (0.15 gm.) of the absolute acid. Koelsch states that workmen may be exposed for years to a 0.02 mg. per liter of air concentration of hydrocyanic acid gas vapor and suffer little injury.

Diagnosis.—Sometimes time is not given for any diagnostic estimate of the cause, the nature of the difficulty being later solved by the pathologist or the chemist. The rapid onset, the odor of the breath, the sudden unconsciousness, the violent convulsions and the peculiar character of the breathing together with the anamnesis usually point with sufficient definiteness to the cause. In no other drug poisoning must a diagnosis be reached more quickly or treatment instituted more promptly if life is to be preserved.

Prognosis.—The mortality rate is very high, ranging from 90 to 95 per cent. If the patient survives an hour the outlook for recovery is more favorable. Recovery has taken place when several times the lethal dose has gained entrance into the body. The amount of the drug ingested or the duration of the exposure to the vapor will determine the outlook for life in a large measure. The possibility of permanent damage to nerve or brain tissue must not be forgotten.

Symptoms.—The symptoms arising after the ingestion of hydrogen cyanid are very prompt and are those of a general protoplasmic poison. This extremely rapid and widespread action which begins almost before the drug has left the mouth ofttimes makes the visit of the physician fruitless because death has already taken place. When smaller doses have been taken the picture is that of an asphyxia due to the inability of the body to utilize the oxygen brought to its tissues by the red blood-cells.

Ewald believes that prussic acid destroys the blood hemase and thus interferes with the liberation of oxygen from its oxyhemoglobin state. Oxygen utilization by the tissues is thus made impossible and, where this action is widespread, the end result is in every way similar to that seen in carbonic oxid poisoning in which the oxygen and hemoglobin union does not take place.

An early very brief stimulation of the vomiting, respiratory, vagus and vasomotor centers with a corresponding functional activity has been described.

Vertigo, headache, palpitation, faintness and convulsions are often the first signs of poisoning. Very early dyspnea is noted which soon becomes urgent. The breathing is peculiar in the fact that the inspirations are short and gasping, while the expiratory time is much prolonged. On the other hand the patient may be found in an unconscious state with pupils dilated, eyes open and staring, weak pulse and gasping, much slowed respirations. Death often is little delayed when the latter picture is presented.

In the so-called apoplectic form of poisoning which takes place when large doses have been swallowed, the patient becomes unconscious almost immediately. Again he may stagger and fall to the ground with glassy and protruding eyes, cold extremities, set jaw, and bloody froth exuding from the mouth. Such a group of symptoms has been mistaken for cerebral apoplexy. In cases surviving for longer periods the body early becomes rigid and the tonic and clonic convulsive states are not long delayed in making their appearance. Death may take place during a convulsion or may be delayed until brought about by exhaustion or a terminal pneumonia.

Mittenzweig reports two cases of cyanid poisoning which survived the initial acute toxemia and later suffered serious after-effects due to irreparable brain injury. These consisted of cephalalgia, cardiac depression, voluntary muscular weakness with moderate reaction of degeneration, sleeplessness, loss of appetite and anemia. The usual early dissolution has permitted but little study of this central nervous system damage.

Preventive Treatment.—The mere mention of the possibilities of poisoning as set forth under the head of "occurrence" ought to suggest preventive measures. The oil of bitter almonds can be freed of prussic acid by treating with an iron salt and distilling. This flavoring extract should be made safe for use by such a purification. It is questionable whether the medicinal use of prussic acid either in concentrated or dilute form is either necessary or justified. The German Government at one time prohibited the use of hydrocyanic acid gas except by the military authorities as a vermin exterminator. This regulation has been modified to permit its use by one company which now has sole control of this practice.

Immediate Treatment.—Treatment must be very prompt. The stomach should be immediately washed with an antidotal solution. These consist of oxidizing agents such as:

1. Hydrogen peroxid, 30 per cent.
2. Potassium permanganate, ¼ to ½ per cent.
3. Sodium thiosulphate, 1 per cent.
4. Ferri hydroxidum cum magnesii oxido.

Of the above, hydrogen peroxid will probably be the choice because of its greater availability. It is said to be especially efficient if the stomach is empty, although the absorption of hydrogen cyanid is so rapid that no antidote is successful. The chemical action of this agent may be expressed as follows:

$$2\,HCN + H_2O_2 = (CO)_2 + (NH_2)_2$$

Martin and O'Brien have made an admirable study of the efficiency of the various supposed antidotal substances in cyanid poisoning. These experimenters conclude that the peroxid of hydrogen is too slow in its action to be of practical use. It is also stated that the presence of the hydrochloric acid in the stomach delays this drug in chemically antidoting the cyanids. Cobalt chlorid ($Co\ C1_2$) has been advised because of the known test-tube formation of cobalt cyanid, a harmless compound, when hydrocyanic acid is brought in contact with this agent. Cobalt chlorid is, however, very toxic and, since the danger of an excess of this preparation is far from negligible, it should not be used. Ferrous sulphate in an alkaline solution produces in the presence of cyanids the feebly toxic ferrocyanids. Since these salts are harmless even in excess, a study of the literature seems to favor their use over other antidotal drugs which have been recommended. Owing to the difficulty of keeping iron salts in solution, Martin and O'Brien recommend the preparation of the following solutions as a means of having this antidote always ready for immediate use.

1. Ferrous sulphate (23 per cent solution)	1 oz. (30 mils) in sealed ampule
2. Potassium hydroxid (5 per cent solution)	1 oz. (30 mils) in sealed ampule
3. Magnesium oxid	30 gr. (2 gm.)
4. Water	250 mils

This mixture will neutralize almost instantly about 5 gm. (0.80 gr.) of potassium cyanid which roughly represents the maximum dose of this poison which is likely to be taken.

Sodium thiosulphate may be used intravenously in 0.5 to 1 per cent solutions with 0.6 per cent sodium chlorid solution. This drug also has been used with some success in 3 per cent solutions given under the skin in amounts of 10 to 16 ounces (300 to 500 mils). Venesection with saline transfusion has its advocates and should be tried if other treatment does not avail.

General.—Artificial respiration by the Schäfer method should be begun at once and continued as long as the heart beats. This will tend to favor the elimination of that part of the drug which is excreted by the lungs.

The weakened heart should be supported by the exhibition of caffein, camphor and atropin hypodermatically. The patient's vital processes may be stimulated by dashing cold water over the face and head and by the continuous inhalation of aromatic spirits of ammonia. External heat should be applied and the heart's power conserved by absolute quietude on the part of the patient.

Finally the physician must bend every effort to remove from the stomach the poison before absorption takes place. This is rarely possible due to the lightninglike speed with which the drug enters the circulation. When absorption has taken place, symptomatic treatment only is indicated. If the ferrous sulphate antidote is immediately available, much good can be expected from its use.

ARSENIC

Occurrence.—Of all the drugs which have been used as homicidal agents, arsenic has without doubt been most frequently chosen. Arsenic as the trioxid, $As_2 O_3$, lends itself to this purpose largely because it is tasteless and practically odorless and can be administered in food without much fear of detection by the victim. Besides being one of the oldest and best known of poisons, it is also a dangerous tool in the hands of the malefactor because its toxic symptoms frequently resemble those which are usually ascribed to certain more or less easily recognized morbid conditions. The writer refers to the similarity between the symptoms of poisoning with repeated small doses of arsenic and those of cholera nostras or of certain food poisonings. Witthaus has studied the motives involved in 1,000 cases of arsenic poisoning with the following rather startling results:

	Per Cent
Homicidal	42.6
Suicidal	23.0
Accidental	20.0
Abortifacient	3.3
Quack medicines	0.4
Motive unknown	10.7

The knowledge on the part of the public of the very toxic nature of this drug makes it, as shown by the above table, not unpopular as a means of suicide.

Rat poisons and insecticides, such as Paris green, London purple or Bordeaux mixture, depend largely on arsenic for their efficacy. The use of this drug by veterinarians, either as a component of soap or as a drug to increase the glossiness of the horse's coat, may lead to accidental poisoning as a result of dishes being used by stable attendants both for the mixing of the drug and for drinking purposes. A solution of sodium arsenite is sometimes used as a weed killer, Willcox reporting 5 cases of accidental poisoning from this source. Solutions of arsenic are also used as a sheep dip and those employed in herding are sometimes accidentally poisoned from the ingestion of this solution.

As a source of occupational disease, poisoning with arsenic is not usually seen in an acute form. Those employed in the mining and scrubbing of certain ores, makers and users of certain dyes and paints, taxidermists and furriers, manufacturers of insecticides, artificial flowers, wall paper, particularly of green color, are sometimes known to absorb arsenic in toxic doses.

Medicinal Use.—The increasing and frequently indiscriminate and ill-advised use of arsenic-containing preparations in the intravenous treatment of syphilis has led to many unfortunate poisonings. Prolonged use of Fowler's solution and other preparations containing arsenic has occasionally resulted in much harm to the patient. Fortunately the quack who attempts to cure cancer by the use of arsenic paste, thereby risking the life of his patient from drug poisoning as well as from his own stupid blundering, is of late less frequently seen.

Food.—In rare instances poisoning has resulted from the consumption of food colored with arsenic-containing dyes, nor should mention of the fact be omitted that beer brewed from dextrose in the manufacture of which impure arsenic-containing sulphuric acid had been used has caused many deaths (Manchester, England, 1901, 7,000 people affected, resulting in 70 deaths). Poisonings have been recently reported as resulting from the ingestion of grapes which were sprayed with Bordeaux mixture (lead arsenate) while still on the vines. The use of arsenic by the professional poisoners of the seventeenth century is only of historical interest to-day. The perfection of chemical methods of detection has done much toward lessening the popularity of this drug as an agent for the destruction of life.

Absorption, Metabolism and Excretion.—Absorption of arsenic from the gastro-intestinal tract occurs readily and to some extent also through the unbroken skin. As a result of this latter fact cosmetic preparations containing arsenic may do harm. The inhalation of metallic arsenic when used in dusts as a fly poison leads to absorption through the respiratory tract.

Arsenic is stored in all the body tissues, especially the liver, kidneys and heart and smaller amounts in the brain and skeletal muscles. There is no detoxicating action of the liver in regard to this drug as poisoning takes place as certainly in dogs from the injection of arsenic into the mesenteric veins as from injection into the jugular. The liver serves only to delay massive entrance into the general circulation. After absorption arsenic is largely found in the blood-corpuscles rather than in the blood-serum.

Arsenic is excreted by the urine, feces, sweat, milk and epithelium. Elimination after administration per orem is largely by the feces; after hypodermic or intravenous injection by the kidneys and skin. After administration per rectum arsenic is said to have been detected in the stomach. Elimination begins from 2 to 8 hours after ingestion and usually requires from 3 to 10 days for completion, although Shepherd states that arsenic was detected in the urine 111 days after 7 doses of neosalvarsan had been given at weekly intervals.

Pathology.—There are no external specific characteristics which denote that poisoning from arsenic has taken place. The skin may be somewhat icteric as a result of a chemical hepatitis. The author has observed 4 cases of an arsenical exfoliative dermatitis following the administration of arsphenamin in which the desquamation resembled that following a severe scarlatinal rash. In a series of 2,600 administrations of arsphenamin, there were two such cases. There are observed abundant evidences of toxic action on the gastro-intestinal tract when the abdomen is opened. A gastritis, toxic in nature, which is seen even though the poisoning is the result of hypodermic injection, is usually present with areas of erosion which may reach the deeper coats of the stomach or intestines. This fact is explained when we remember the active excretory rôle played by the gastric mucosa. Frequently in the large intestine the mucous membrane is removed from more or less extensive areas as a result of a toxic necrosis, these changes taking place within two or three hours in animals after subcutaneous injection. The intestines may contain large quantities of the so-called "rice water" fluid. There is usually seen a fatty degeneration with cloudy swelling and proliferation of cells of the hepatic parenchyma, although these changes are rarely as marked as in phosphorus poisoning. The kidneys show the presence of a nephritis in which both the vascular and tubular elements share. The tubules are usually found to be full of hyalin droplets and degenerated epithelial débris.

Ecchymoses in the left ventricular myocardium are not infrequently seen and are thought by some observers to be peculiar to arsenic poisoning. Finally, there is often a great variance between the antemortem clinical picture and the presence of inflammatory changes postmortem.

Fatal Dose.—The lethal dose varies with the solubility of the preparation and the individual idiosyncrasy of the patient. Of the trioxid 2 to 5 gr. (0.1 to 0.3 gm.) is usually fatal, but recovery has occurred after much larger quantities have been ingested, probably due to the early rejection by the stomach. Death has taken place within twenty minutes after the ingestion of a massive dose but its time may vary from three days to as many months.

General Symptoms.—It has been tersely said that it is not the amount of arsenic found in the stomach contents or the urine from which we can judge the danger to the patient's life, but that it is the amount *not* found there that really matters. The amount of drug ingested will often determine the amount which quickly finds its way out of the body, but it is the drug which has entered the blood-stream and serous fluids that must be combated by treatment. Individual idiosyncrasy seems to play a rather prominent part in poisoning by arsenic. This is well shown by the sharp reactions sometimes seen after the intravenous exhibition of 14 gr. (0.9 gm.) of neo-arsphenamin in the treatment of lues. It should be understood that the symptoms described below are those typically seen, but that for reasons difficult to understand the gastro-intestinal symptoms may be conspicuous either by their exaggeration or by their absence.

Immediate Symptoms.—The early symptoms which usually arise in from ten to sixty minutes after ingestion are chiefly referable to the gastro-intestinal tract except where almost immediate death follows the inhalation of the fumes of arseniurated hydrogen which is a very potent poison. The patients usually first experience faintness with a feeling of heat and constriction of the throat, thirst, nausea, vertigo and a burning pain in the stomach exaggerated by pressure. The vomiting is violent and persistent, the temperature subnormal, the pulse small and rapid. A most profuse and persistent diarrhea soon develops and the dejections, which at first consist of the contents of the large bowel, soon become yellowish or greenish in color and later serous and contain mucoid flakes and more or less fresh blood. This stool has been likened in appearance to the "rice water" stool of cholera. The tenesmus is extreme and the abdominal distention and cramps only serve to further prostrate the patient. The vomitus consists at first of stomach contents and later bits of stomach mucosa ofttimes streaked with blood are seen. Violent cramps in the legs and thighs are often most distressing to the patient.

A marked myocardial poisoning is shown by a small and frequent pulse, cyanosis and icy extremities. The respirations are difficult and repressed on account of the presence of extreme abdominal tenderness. As the prostration increases the patient may lapse into coma which not infrequently presages early dissolution. Convulsions, tonic or clonic in character, occur. The urine contains albumin and sometimes blood, is scanty and there may be a troublesome dysuria. Collapse due to continued vomiting and purging, with cold moist skin, thready pulse, cold extremities and sometimes convulsions, is of gravest portent even though the mind is clear.

At times when the amount of drug taken has been small, although the initial symptoms have been stormy, improvement seems to take place after a few hours. The purging and vomiting lessen and the acute pain abates. But the cardiac distress, the extreme dehydration and prostration persist and the kidneys do not reëstablish normal function. Fever develops, abdominal pain, dyspnea and diarrhea reappear and convulsions and death close the scene. Again some writers have described a form of delayed arsenical poisoning which makes its appearance days or weeks after the administration of arsphenamin and which is characterized by jaundice and an intense and often fatal toxemia. The author has seen one such case which occurred two weeks after the conclusion of a series of five arsphenamin injections.

Sequelæ.—Even when the patient survives the acute symptoms, a neuritis affecting the peripheral nerves, with consequent paralysis which is preceded by tingling, numbness and various parasthesias, may occur. The lower extremities are more often affected than the upper and the extensors more than the flexors. Terminal dementia has been reported. In nonfatal cases prolonged and obstinate disturbance of the gastro-intestinal functions persists. Usually myocardial integrity is never restored and muscular weakness and anemia are distressing after-effects.

Diagnosis.—The diagnosis rarely presents any difficulties. Precise analytic measures are of value in solving medicolegal problems. The anamnesis, the mental state of the patient in suspected suicidal poisonings and the symptoms of the onset of the gastro-intestinal disturbances enumerated above are usually sufficient to enable the physician to make a correct diagnosis. The analysis of food eaten and the isolation of arsenic from the vomitus, stools and urine is conclusive evidence of poisoning.

Prognosis.—The liability of grave sequelæ must be borne in mind in arriving at any reasonable prognostic estimate. Death in the majority of cases occurs in from eight to twenty-four hours while, on the other hand, a dreary and painful existence may have to be endured for weeks, months or even years. The mortality even when early treatment has been instituted is conservatively placed at about 50 per cent.

Cohn believes that the permeability of the kidneys modifies the body reaction in arsenic poisoning, a contracted kidney increasing the danger to the patient.

General Treatment.—When the physician is confronted with a patient whose history and symptoms point toward an arsenic toxicosis, he must realize that here as in most poisonings the law obtains that the chances for recovery are in direct proportion to the promptness of removal or neutralization of the drug taken. Three important considerations present themselves:

1. The early removal of the drug from the gastro-intestinal tract is of greatest importance.

2. Mechanical means are more trustworthy than procedures which depend for their efficacy upon chemical neutralization or the change to an inert substance of the poison ingested.

3. The treatment instituted must be continued and not represent only one attempt. It should include both mechanical and chemical measures and should be founded on known facts as to absorption, fate and excretion of the drug.

Immediate Treatment.—No time must be lost in procuring the generally accepted U. S. P. antidote, ferri hydroxidum cum magnesii oxido. A messenger should be dispatched to the nearest pharmacy for this preparation which should be kept freshly prepared for emergency use by every druggist. In the meantime the following measures should be carried out:

1. Immediate lavage of the stomach with warm water or with a 2 per cent solution of sodium bicarbonate. This lavage should be repeated frequently and the amount of solution used must be sufficient to distend the stomach mildly. Crystals of white arsenic or Paris green adhere to the gastric mucosal folds tenaciously and every effort must be made to cleanse the rugæ mechanically before absorption or necrosis takes place. If in the meantime the antidote has been procured, give from 3 to 4 ounces (90 to 120 mils) of this preparation. If the antidote is not available, milk, albumin water or mucilaginous drinks such as flaxseed tea or slippery elm tea in free amounts may be administered. The cleansing of the stomach should be thoroughly and painstakingly accomplished.

2. Cleansing of the lower intestinal tract should be given as much attention as the gastric lavage. To this end a rectal tube should be inserted as high as possible in the lower bowel without kinking and by means of warm water or sodium bicarbonate solution a thorough flushing of the large intestine should be accomplished. This process should be repeated three or four times at three-hour intervals.

3. After gastric lavage has been practiced three or four times at hourly intervals, and if the official antidote solution has been procured and a portion of the fluid used has been left in the stomach on each occasion, attention may be given to cleansing the upper bowel. For this purpose either castor oil or a saline purgative may be used. If the latter is selected, 2 to 4 ounces (60 to 120 mils) of a saturated solution of magnesium sulphate should be passed through the tube and left in the stomach.

4. Attention should be given to general symptomatic indications. If shock exists, appropriate treatment is indicated, such as external heat, cardiac support and morphin sulphate in small doses, to control the pain.

The latter drug should be used cautiously so as not to delay intestinal excretory action. Adrenalin chlorid in moderate dosage, 1/64 gr. (0.001 gm.) has been advised. Dehydration plays a not unimportant rôle in the production of collapse. Saline infusion or hypodermoclysis is strongly indicated to meet this lack of fluids.

5. Emetics, although less effective, are to be used when the stomach tube is not at hand. Warm water and mustard, zinc sulphate in dosage of 15 gr. (1.0 gm.), tartar emetic, 2 gr. (0.13 gm.), and apomorphin hydrochlorid, 1/10 gr. (0.006 gm.), hypodermatically, have been advised. The latter two drugs should be used cautiously because of the already great prostration of the patient.

General Considerations.—Difficulty is often encountered in controlling the diarrhea following arsenic poisoning. Opium, bismuth or chalk should not be used too early for fear of embarrassing elimination by way of the intestines. Repeated administration of a saline seems to be safe. The diet should be largely composed of milk or gruels and liquids in large amounts continued.

Official Antidote.—Ferri hydroxidum cum magnesii oxido is prepared by adding a suspension of magnesium oxid to an iron sulphate solution. The following equations will express more clearly this reaction:

$$MgO + H_2O = Mg(OH)_2$$

$$Fe_2(SO_4)_3 + 3Mg(OH)_2 = 2Fe(OH)_3 + 3MgSO_4$$

This solution changes the actively poisonous arsenous preparations into the more insoluble and less toxic arsenic compounds as follows:

$$3As_2O_3 + 2Fe(OH)_3 = 2Fe(AsO_2)_3 + 3H_2O$$

The antidote may be administered in large quantities but should be removed from the stomach at once to rid the body of the less harmful arsenic compound. The latter is about one-half as soluble as the arsenous preparations.

Ferric hydroxid may also be prepared by precipitating ferric chlorid or sulphate solutions with ammonia water and washing the precipitate with water to remove the ammonium chlorid or sulphate.

Sollmann deprecates the use of chemical antidotes. Experimentally the hypodermic administration of magnesium sulphate has protected animals from fatal doses of arsenic, a non-soluble compound being formed.

PHOSPHORUS

Occurrence.—There are two common forms of phosphorus, the transparent or white phosphorus which is the type formerly found in matches and which is very poisonous, and the red phosphorus which in the pure state is not harmful to the human body if swallowed. Matches are usually manufactured by dipping the stick into a mixture of sulphur and glue and then tipping the ends with a mixture of phosphorus and potassium chlorate. The phosphorus in safety matches is on the side of the box. Alarming if not fatal poisoning has resulted in children from sucking the ends of matches. Since 1906, however, poisonings from the white phosphorus of matches have been rapidly reduced. In that year at a conference of representatives of a number of European powers held in Berne, Switzerland, a resolution was adopted prohibiting the use of white phosphorus in the match industry. In 1912 the United States Congress levied a tax of two dollars per hundred on white phosphorus matches and provided heavy penalties for importing or exporting the same. This legislation almost completely removed the danger of poisoning from this source.

Poisonings by phosphorus are largely accidental in this country. Von Jaksch states that in Prague and Vienna a large number of suicidal poisonings by this drug come under the physician's observation.

Absorption, Metabolism and Excretion.—Absorption of phosphorus, which is usually slow, takes place from the intestinal canal and to some extent through the alveolar endothelium after inhalation of the phosphoric vapor. Commercial phosphorus is not readily soluble in water and volatilizes very slowly at body temperature so that, unless it is well broken up before it is swallowed, there may be very little of the poison absorbed even though a massive dose has been taken. On the other hand, phosphorus is easily dissolved in fats or oils and should by any chance these substances be brought together absorption is very much hastened. As a result of this tardiness in absorption toxic symptoms are usually delayed several days after ingestion.

Oxidization within the body is likewise not rapid. Our knowledge is very imperfect as to the exact change which this drug undergoes in the body. It is known, however, that it requires days for oxidization to take place in the stomach and intestines. Wood believes that phosphorus passes into the blood-stream unchanged and not as phosphoric acid or other compound. It has also been shown that while phosphorus to some extent is converted into phosphurated hydrogen in the alimentary canal, this action takes place to a greater degree in the venous blood-stream. The arterial current therefore receives this drug partly unchanged and partly as phosphoric acid and phosphurated hydrogen. It has been suggested by Simonds that phosphorus may reverse the action of the intracellular ferments.

Phosphorus is excreted as hypophosphoric acid or unchanged phosphorus in the urine and stools and possibly through the gastric mucosa. Elimination is not prompt as phosphorus has been found in the feces three and one-half days and in the vomitus two days after poisoning.

Pathology.—In severe acute poisoning the pathologic changes resemble those of acute yellow atrophy of the liver. There is evidence everywhere of a lowered metabolic rate. The body of the patient who has died as a result of a phosphorus poisoning may display an icterus of slight or severe grade. On opening the abdomen the garlicky odor of phosphorus is often detected. The liver is seen to be enlarged and yellowish in color. There is noted a deposition of fat in smooth and skeletal muscles, heart, kidneys and blood-vessels. The increased fat in the liver is probably drawn from other parts of the body so that the total body fat is not thus increased. The blood is tarry and coagulates with difficulty. Multiple hemorrhages, either petechial or more extensive in character, may be seen in the skin, mucous membranes, lungs and other viscera.

Fatal Dose.—The toxicity of phosphorus depends somewhat on whether the dose taken existed in a divided state or whether it was not broken up. Death may be caused by a minimal dose of less than 1 gr. (0.05 gm.) but the lethal dose is usually twice that amount. The ingestion of the phosphorus in sixteen match heads has caused death in an adult while a small child has suffered a fatal poisoning from two matches. There is reported the death of a lunatic from eating 1/10 gr. (0.006 gm.) of white phosphorus.

Symptoms.—The symptoms of phosphorus poisoning may be divided into immediate and secondary. Because of the relative insolubility of phosphorus, the former do not make their appearance at once if the drug gains entrance to the body through the alimentary tract. Especially are these early symptoms delayed if the stomach contains food when the drug is swallowed. In from three to ten hours the patient usually complains of weakness, nausea and a burning pain in the epigastrium which later becomes general. Emesis soon follows, the vomitus being green or resembling coffee grounds in color and presenting the odor of phosphorus (garlic). At times material constituting the vomitus and stool may be phosphorescent when examined in the dark. The likelihood of detecting phosphorescence is enhanced if the substance to be tested is acidified by sulphuric acid and warmed in a shallow dish. There may be an early profound depression of the myocardium and death has taken place promptly from this cause. Usually, however, the local gastro-intestinal symptoms have almost disappeared before the more serious secondary phase develops.

The period of secondary symptoms presents the picture of a very grave toxemia to which signs of a metabolic change incident to interference with the so-called internal respiration are added. According to Jacoby, who worked with dogs poisoned with phosphorus, this drug destroys the hepatic cells but not their autolytic enzymes, thus favoring autolysis.

A conjunctival icterus is frequently noted on about the third day. The jaundice deepens rather rapidly until the most extreme yellowing of the skin takes place. The abdomen is distended and tender to palpation, particularly in the right hypochondrium. The physician soon discovers that the hepatic edge is to be felt two or three fingers breadths below the costal margin. This enlargement of the liver takes place very rapidly. The tongue is coated and the breath fetid. The vomiting which may have ceased for from twenty-four to forty-eight hours returns in an aggravated form. The stools are soft and ofttimes stained with blood. The pulse is small and irregular but not greatly accelerated.

The mental symptoms do not usually develop until after the jaundice has appeared. Prostration is profound. Insomnia, mental anxiety, headache and delirium of an erotic nature are observed. On the other hand, in fatal cases consciousness may be preserved until just before death. Convulsions have been regarded by most writers as a most unfavorable omen. Nitrogenous and carbohydrate metabolism is greatly altered in phosphorus toxemias. There is a marked increase in urinary nitrogen and the excretion of phosphates and sulphates is also increased. There may or may not be a proportional increase in the urea elimination but the ammonia output is rather constantly affected. Phosphorus causes a disappearance of glycogen from the liver. There is but little doubt that the production of glycogen is delayed or prevented by this drug or that its consumption is increased or both.

The urinary findings are quite constant. The urine is scanty, acid in reaction, dark brown in color from the admixture of bile and blood and contains both albumin and casts. Due to deficient oxidization an excess of organic acids is noted. Leucin, cystin, tyrosin and sarcolactic acid have been found in the urine. Sugar has been found in the urine in poisoning by this drug.

As prostration deepens, the respiration becomes more difficult, the temperature subnormal and the pulse thready and rapid. Multiple hemorrhages may appear on the skin and mucous membranes as death closes the scene.

Diagnosis.—The history of ingestion of the drug as set forth earlier in this description, the chemical characteristics and the odor and luminosity of the vomitus usually make errors in diagnosis unlikely. Acute yellow atrophy of the liver is sometimes confused with late phosphorus poisoning. The ecchymoses and digestive disturbances in the absence of other facts might lead to a mistaken diagnosis of scurvy. The mention of these possibilities ought to be sufficient to put the physician on his guard.

Prognosis.—Phosphorus is not a rapidly fatal poison. Death does not usually take place earlier than from two to five days, although a case is reported in which death occurred in thirty minutes after poisoning. If the patient survives the acute poisoning, the return to health is slow and difficult. The average mortality may be conservatively placed at

50 per cent. When massive doses are ingested or employed as an abortifacient the death-rate mounts rapidly.

Preventive Treatment.—Matches make poor playthings for children both from the standpoint of the danger of poisoning as well as from the risk of fire. Those employed in the match industry should be protected from the vapors of phosphorus. Rigid observance of the rules of personal hygiene should be required of all those who work with phosphorus. The writer has reference to the necessity of dental hygienic measures being enforced as well as the cleansing of the hands before food is consumed. Suicides from the use of phosphorus while rare are difficult to prevent.

Immediate Treatment.—Even though the oxidization and absorption of phosphorus in the alimentary tract is somewhat delayed no time must be lost in beginning treatment. The following measures should at once be carried out:

1. If copper sulphate is procurable, give at once 1½ to 3 gr. (0.1 to 0.2 gm.) in 3 ounces (90 mils) of water every 10 minutes until vomiting takes place. Avoid oils, fats and milk as absorption is said to be hastened by their use.
2. If copper sulphate is not at hand, gastric lavage with other oxidizing agents such as warm potassium permanganate solution, 1:1,000, or hydrogen peroxid, 2 per cent, should be given.
3. If none of the above agents is at hand use large quantities of warm water which is always available. If no stomach tube is to be procured, require the patient to drink copious amounts of warm water or a 5 per cent solution of sodium bicarbonate until emesis results.
4. A saline cathartic such as magnesium sulphate, 2 to 4 ounces (60 to 120 mils.) should be administered. This solution may be passed through the tube following the lavage.

Secondary Stage.—The above measures are chiefly to accomplish removal of the drug from the stomach and to prevent its absorption.

When the acute gastro-intestinal symptoms are past, the treatment must be largely centered on meeting the therapeutic indications as they arise, since it is evident that no known treatment can remedy the widespread tissue destruction when once it has occurred.

Sodium bicarbonate solution (2 to 5 per cent) by mouth, bowel or in the vein is useful in combating the acidosis and stimulating renal function. The toxic depression should be met with supportive measures. Digitalis by hypodermic injection may be required to support the lagging heart. For the nervous symptoms, sodium bromid in doses of from 10 to 20 gr. (0.64 to 1.24 gm.) every third hour or morphin in doses of ¼ gr. (0.016 gm.) may be required. The purging may be somewhat alleviated by mucilaginous drinks, but drugs which delay intestinal elimination should be used only with caution.

Special Therapy.—In 1868, Audaut, a French physician, proposed the use of the oil of turpentine in the treatment of phosphorus poisoning. Reports are very contradictory as to success in its use, probably due to a misunderstanding as to the kind of oil which is most efficacious. Of the three kinds of turpentine in European commerce, namely, the rectified, German and the French, the acid French oil forms with phosphorus the harmless turpentine-phosphoric acid. Ordinary American turpentine has no value in phosphorus poisoning. If the amount of drug taken is known, 100 parts of oil for every 1 part of phosphorus taken may be administered or, if this information is lacking, 7½ gr. (0.5 gm.) may be administered three or four times a day for a week. A search of the literature seems to prove that this treatment is less efficient than is the administration of copper sulphate.

Atkinson has endeavored to find an oily substance which will aid in removing the clinging particles of phosphorus and thus assist in hastening elimination without the oil itself being absorbed together with a portion of the phosphorus in solution. He states that liquid petrolatum in generous doses will perform this function and urges its use. Liquid petrolatum may be used as a lavage as well as an agent to be left in the intestinal canal. Encouraging animal experiments are cited by this writer.

General Therapeutic Comment.—Copper sulphate acts as a prompt emetic and is said to oxidize the phosphorus and envelop its globules with a coating of reduced copper which delays absorption. It should not be forgotten that this drug is itself toxic in large quantities and may thus do harm. The action of other oxidizing agents, such as hydrogen peroxid and potassium permanganate, is to dislodge particles of phosphorus adherent to the mucous membranes so that they will be vomited or washed out of the stomach.

The introduction of oxygenated water into the stomach and the forced inhalation of oxygen has been advised, but sufficient proof is wanting to justify a substitution of these measures for those mentioned above. Doubtful measures merit only secondary or supplemental use.

Simonds, as a result of animal experiments, believes that the feeding of sugar to patients poisoned by phosphorus is indicated. He concludes that not only would an easily oxidizable food be thus furnished, but that the supplying of glycogen to the liver protects against the grave phosphorus toxemia and favorably affects protein metabolism. This writer suggests that by preventing a reversal of the action of the intracellular enzymes autolysis would be lessened.

Finally the efforts of the physician must, above all, be directed toward bringing about early removal of the drug before absorption and consequent tissue degeneration takes place.

METHYL ALCOHOL
(CH_3OH)

(Methanol—Wood Alcohol—Columbian Spirits—Wood Naphtha—Hastings Spirits—Carbinol—Methyl Hydroxid—Methylic Hydrate)

Occurrence.—Methyl alcohol is a colorless volatile liquid manufactured in this country by the destructive distillation of wood. In Europe methanol is procured from peat and also as a by-product in the manufacture of wood pulp. Prior to the recent Federal Enactment relating to the manufacture and sale of ethyl alcohol and beverages containing this substance, poisonings by methyl alcohol were largely limited to the field of industrial medicine. It is true that unscrupulous or ignorant manufacturers of flavoring and medicinal extracts sometimes used this drug as a menstruum or diluent to ethyl alcohol because of its being relatively less expensive. The Pure Food Act of 1906 partially removed the danger of its use in manufacturing such pharmaceutical preparations as essences, balsams, extracts, Jamaica ginger and so forth. When alcoholic beverages became more expensive and difficult to obtain, a veritable epidemic of poisonings from wood alcohol took place. Until a thirsty public became aware of the existence of another and not easily distinguishable alcohol besides the one which longer or shorter acquaintance had made familiar, many lives were lost and, if life was preserved, sight was usually affected. Buller and Wood in 1904 reported that the literature disclosed 153 cases of blindness and 122 deaths prior to that year due to this agent.

Prior to 1906 ethyl alcohol was not largely employed for industrial purposes such as the production of heat, light or power because the payment of the federal tax prevented its use from an economic standpoint. In June of that year by act of Congress the sale of this alcohol without the payment of a tax was authorized. In order to prevent its use, however, for beverage or medicinal purposes, certain drugs were required to be added which from their odor or taste would prevent its use for any but industrial purposes. One of the favorite formulæ used for this denaturing has been the addition of 10 per cent methanol and ½ per cent benzene. These agents were intended to give to the mixture a nauseating odor and taste from which even the most depraved inebriate would shrink. This did not prove the case and it therefore became necessary, in order to prevent ignorant self-destruction, to reduce the amount of methanol allowed in denaturing formulæ to 2 per cent. This was done in January, 1920.

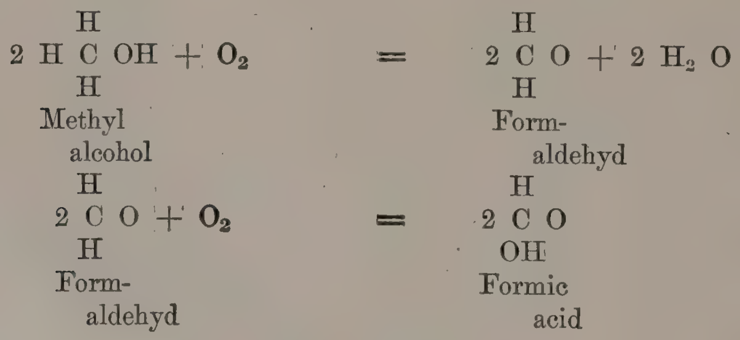
In Berlin, in 1911, 89 deaths and 5 cases of blindness occurred as a result of a drinking bout at which a wood alcohol containing beverage was consumed. In New York City during the year 1919 there were 54 deaths from wood alcohol poisoning, 19 of which occurred in the month of December. The Health Department of New York has forbidden the use of wood alcohol in any preparation either for internal or external use. It is estimated that 81,000,000 gallons of methyl alcohol are manufactured in the United States annually and that 2,000,000 people are employed at trades in which it is used. Baskerville summarizes the legitimate uses of methyl alcohol as follows:

1. For denaturing ethyl alcohol.
2. In the chemical laboratory as a solvent, reagent and extracting agent; also in the manufacture of formaldehyd.
3. In certain pharmaceutical preparations.
4. In the arts and crafts.
5. As a fuel and in cleaning fluids.

Accidental poisoning may result from the ingestion of methanol by those persons brought in contact with it in any of the above industries. The vapor of wood naphtha is capable of doing harm when inhaled and it is stated that a 0.2 per cent concentration in air is dangerous.

Absorption, Metabolism and Excretion.—Methyl alcohol is absorbed through the alveolar endothelium, through the skin and rapidly through the gastro-intestinal mucous membranes.

Methyl alcohol is slowly and incompletely oxidized in the body. Unlike ethyl alcohol, which is promptly and completely changed to carbon dioxid and water, wood alcohol gives rise to formaldehyd and formic acid. Mayer states that formaldehyd and formic acid are respectively thirty-three and six times more toxic than methanol from which they are derived. The oxidization processes which take place may be more clearly understood by referring to the following chemical formulæ and equations:



$$\underset{\text{Methyl alcohol}}{2\ \text{H}\overset{\text{H}}{\underset{\text{H}}{\text{C}}}\text{OH}} + O_2 = \underset{\text{Formaldehyd}}{2\ \overset{\text{H}}{\underset{\text{H}}{\text{C}}}\text{O}} + 2\ H_2\ O$$

$$\underset{\text{Formaldehyd}}{2\ \overset{\text{H}}{\underset{\text{H}}{\text{C}}}\text{O}} + O_2 = \underset{\text{Formic acid}}{2\ \overset{\text{H}}{\underset{\text{OH}}{\text{C}}}\text{O}}$$

Of the greatest therapeutic importance is the fact that, on account of the slow oxidization and excretion of methyl alcohol, there exists a clearly demonstrable cumulative action. Methanol and its products are eliminated by means of the kidneys, gastric mucosa and the respiratory tract. Bongers gave methyl alcohol to dogs and recovered three times as much by gastric lavage on the second and third days as he did on the first day after poisoning. Palmer and Harrop have also shown that the gastric mucosa plays an important excretory rôle. They state that as much as 10 per cent of the total amount of alcohol taken by mouth can be recovered by repeated gastric lavage twenty-four hours after ingestion. Small amounts of wood alcohol have been recovered from the stomach as late as the seventh day. Osser recovered in dogs 55.8 per cent of the total dosage from the expired air. Pohl was unable to recover the unchanged methyl alcohol from the urine. When given by bowel unchanged methyl alcohol can be procured by lavage of the stomach for several days.

Pathology.—The postmortem findings in cases of wood alcohol poisoning have few constant characteristics. There is usually congestion and sometimes small hemorrhages occur in the mucous membranes of the stomach, duodenum and bladder. The kidneys are swollen and actively congested. The optic changes consist of hyperemia and edema of the fundus and an inflammation and later atrophy of the optic nerve. Methyl alcohol has been detected in the tissues six days after its ingestion. Eisenberg states that in rabbits after the inhalation of wood alcohol there were rather constant cerebral degenerative changes. Barbash has seen a case in which thrombosis of the brachial, radial and ulnar arteries took place after methanol poisoning. Isaacs states that the blood is chocolate in color and that he has proved by means of the spectroscope the existence of methemoglobin, although Rabinovitch was unable to demonstrate the presence of this body.

Fatal Dose.—The lethal dose of wood alcohol is probably from 100 to 250 mils. Due to its apparent cumulative action fatal poisonings may result from smaller doses frequently repeated.

General Symptoms.—To the casual observer, the symptoms resulting from the imbibition of methyl alcohol may appear identical with those occurring in intoxication with ethyl alcohol. Due to this fact and to the convivial atmosphere usually associated with the consumption of alcoholic beverages, cases of methyl alcohol poisoning may go unrecognized and untreated for some hours and valuable time be lost. Then too, unfortunately for the patient, the typical symptoms may not appear for several hours or sometimes even two or three days after the drug has been taken. There is usually a much more violent gastro-intestinal reaction than is seen after the consumption of grain alcohol. Nausea and vomiting, vertigo, headache and general weakness are early symptoms. The narcosis is deep and prolonged and indeed it is this latter fact that often attracts attention to the unusual nature of the case. The onset of coma is often delayed as compared with that produced by ethyl alcohol but unconsciousness is likely to continue for a much longer period. It may be generally stated that stupor in ethyl alcohol poisoning rarely lasts longer than twenty-four hours, while that from methanol may last from forty-eight to ninety-six hours. In toxemias of a severe grade, collapse with dyspnea, intense cyanosis and deepest coma occur, followed by speedy dissolution without the patient regaining consciousness.

Eye Symptoms.—Not infrequently after the recovery from what has apparently been the usual alcoholic narcosis, the patient is first alarmed by the realization that his vision is impaired. If recognition of the real difficulty has not taken place until optic symptoms develop, the efficacy of treatment is doubtful. While unconsciousness is present the pupils are usually dilated and respond to light sluggishly if at all. Nystagmus may be present. The optic injury is bilateral and consists of dimness of vision or even total blindness. The loss of vision may develop in a few hours after poisoning or may not appear for three or four days. There may be some improvement but return to normal is not usual and relapse to permanent total blindness is the rule where large doses of wood alcohol have been absorbed. Massive absorption, however, is not always necessary to produce grave damage to the optic nerve, for blindness has been reported to occur when only 10 mils of wood alcohol have been ingested, while 90 mils have caused no injury of sight in other cases. Permanent impairment of sight occurs in about 50 per cent of all cases.

In a case reported by Rabinovitch the patient, a woman seventy years of age, drank a "glass" of wood alcohol, presumably 6 or 7 ounces, with suicidal intent. Death took place in six days. There were early and marked evidences of nitrogenous retention, the uric acid, urea and creatinin registering 9.3, 144, and 4.5 mg. per 100 mils of blood respectively. Acute parenchymatous changes were found in the kidneys at autopsy. An acidosis was present clinically, the carbon dioxid combining power of the blood plasma being 46 per cent and later, just before death, 26 per cent.

Acidosis.—Tyson and Schoenberg, Harrop and Benedict and others have shown that in poisoning with methyl alcohol there is usually a definite lowering of the blood alkali reserve. The existence of an acidosis is shown chemically by a decreased titratable alkalinity of the body fluids as well as by a lowered carbon dioxid combining power of the blood-plasma and a lowered carbon dioxid tension in the alveolar air. Clinically this condition manifests itself by nausea, irritability, hyperpnea and coma. Numerous theories have been offered to explain its existence. This acidosis can probably be explained in part at least by the production of formic acid as an oxidization product and by the action of formaldehyd on neutral ammonia salts. Rabinovitch suggests that the action of formaldehyd on amino-acids may result in the formation of methylene derivatives which are strongly acid in nature.

Nitrogenous Metabolism.—There is a difference of opinion concerning the effect of wood alcohol poisoning upon nitrogen metabolism. A great increase in blood urea, creatinin and uric acid is noted by some writers while others observe but negligible variation from the normal. In the case recently studied by Harrop and Benedict, a woman twenty-five years of age, there was no increase in concentration of the blood nitrogenous bodies. The marked difference in age between this patient and that of Rabinovitch, mentioned above, should not be overlooked, although impaired kidney integrity might explain the apparent difference. The urine usually contains albumin in abundance and casts both hyalin and granular when toxic doses of wood alcohol have been taken.

Diagnosis.—The diagnosis can usually be made from a consideration of the history of a drinking bout in which alcoholic beverages of doubtful nature have been consumed, the early and prolonged narcosis, the optic signs and the chemical analysis of the urine revealing the presence of formic acid. The detection of methyl alcohol through lavage of the stomach is conclusive evidence. Acute abdominal distress followed by stupor and a disturbance of vision point definitely to wood alcohol poisoning.

Prognosis.—Marked difficulty is encountered in endeavouring to predict the outcome in so far as life is concerned, for the mortality rate does not always vary directly with the quantity of wood alcohol taken. Permanent damage to the optic nerve occurs in one-half of the cases. The fact that the advent of blindness is often delayed in making its appearance should not be forgotten.

Prophylactic Treatment.—Preventive treatment in so far as industrial poisonings are concerned should be effectual. The proper safeguarding of the health of the employees of manufacturers of wood alcohol and of those engaged in paint, varnish and other industries would seem to require proper ventilation of work rooms and the prevention of the absorption of wood alcohol through the skin.

The use of methyl alcohol in the preparation of foods and drugs should be prevented by proper legislation. The use of wood alcohol in the preparation of cosmetics or other toilet articles for external use should be prohibited. While advice from the physician as to care in choosing the type of alcohol to be consumed as a beverage will usually be largely wasted, yet the effort should be made to disseminate information as to the frequent presence of methyl alcohol and its great danger. To many "alcohol" means drink and the addition of the word "wood" deprives the article of none of its attractiveness. It is regrettable that methyl alcohol was ever deprived or its former nauseating, vile odor and taste by deodorization processes. The real danger of using methyl alcohol to rub the skin after a bath or for external application in any other way should be emphasized.

Immediate Treatment.—Evacuation of the stomach contents is first of all to be accomplished by the use of the stomach tube. Gastric lavage should be practiced, using a 1 to 2 per cent solution of sodium bicarbonate. If no tube is available, an emetic should be promptly administered or large quantities of sodium bicarbonate solution should be given until emesis takes place. The lower bowel must be thoroughly cleansed, using warm water or the alkaline solution mentioned above. Gastric lavage with an alkaline solution should be repeated two or three times a day for several days after poisoning because of the fact that the stomach excretes wood alcohol in small quantities for some time.

General Treatment.—External heat is indicated for the shock frequently observed after acute poisoning. The exhibition of respiratory and cardiac stimulants is often necessary. To combat the acidosis which is always present, large amounts of alkalis should be given. Sodium bicarbonate, which is probably to be favored, may be given in dram (4 mils) doses every three hours for the first day. When the stomach is not retentive this drug may be given intravenously in 5 per cent solution or by the bowel by the drip method. If given intravenously care should be taken in preparation and sterilization, since frequently by the open sterilization method, carbon dioxid gas having been driven off by the heat, sodium carbonate is the drug actually introduced into the blood-stream and sometimes rather alarming results follow. Large amounts of water should be given. The following useful combination may be given every three hours:

Potassium bitartrate	1 dram	(4 gm.)
Sodium citrate		
Sugar	āā ½ dram	(2 gm.)
Lemon juice q. s.		
Water	8 ounces	(250 mils)

Continuous alkaline enteroclysis is to be favored. The urine should be kept alkaline to methylene-red.

If symptoms of optic neuritis develop, strychnin is indicated and potassium iodid in 10-gr. (0.64-gm.) doses may be prescribed. Zethelius has treated acute eye symptoms in 3 cases of methanol poisoning by spinal drainage repeated at intervals of from five to eight days for several weeks. He reports 1 case as being cured and 2 as showing improvement. It would seem that, if spinal drainage is to be efficacious, this procedure should be instituted promptly after the diagnosis has been made. The treatment of visual defects when once established usually offers but little encouragement. While this procedure has little to commend it, on a rational basis, yet any treatment which offers a ray of hope, to prevent irreparable damage, should be given a fair trial until definitely proven of no value.

NICOTIN

Occurrence.—Nicotin is the active principle of tobacco and is no longer recognized by the United States Pharmacopœia as of use in the practice of medicine. It is a very volatile alkaloid with an unpleasant penetrating odor, a strong burning taste and as transparent as water but becoming dark on exposure to light. The best Havana tobacco contains about 2 per cent of nicotin while other varieties may contain from 7 to 10 per cent of the alkaloid. It is of such toxicity that death has resulted in three minutes after a massive dose was taken. Children have been poisoned as a result of playing with old pipes and in the medical literature not a few deaths are reported as a result of this accident. There are on record two fatal poisonings from excessive smoking, seventeen and eighteen pipes being consumed consecutively. Death has occurred as a result of inhaling too much snuff. An infusion of tobacco was formerly employed as an enema in the treatment of pin-worm. Garvin reports the death of a child six and one-half years old forty-five minutes after the exhibition of less than 22 gr. (1.5 gm.) of tobacco in an enema for this purpose. The ingestion of large quantities of the leaves or the infusion of tobacco has been responsible for fatalities among the mentally deranged. Reynolds has observed an unusual fatality as a result of tobacco accidentally falling into food which was warming on the stove.

Feil reports a death as a result of swallowing a nicotin plant spray. Serious poisonings have followed the application of an infusion of tobacco to extensive lesions and harm may result from the use of the wet leaves of tobacco in a poultice for local inflammatory conditions. Appolzer describes a poisoning as the result of a tobacco smoker going to sleep with a cigar in his mouth. McNally has reported 12 deaths arising from nicotin ingestion which have come under his observation. Of this number 5 drank a solution containing the alkaloid in mistake for whisky, 1 in mistake for cascara sagrada and another in mistake for cough syrup. Three used this drug as a means of accomplishing self-destruction, while in 1 case the motive was not determined. In the last case in the series a solution of nicotin was criminally used to bring about an abortion. Commercial insecticide preparations which are further diluted before use contain from 8 to 44 per cent of nicotin.

Absorption.—Nicotin is absorbed very rapidly from mucous membranes and especially so through the alveolar endothelium. Absorption as a result of hypodermic injection and through the unbroken skin is somewhat less rapid, especially in the latter instance. Death has resulted, however, through this latter avenue of absorption.

In 1912, Dixon and Lee apparently confirmed the old belief that the liver destroys at least a part of the nicotin brought to it, but Clark in the same year was not able to confirm this fact by animal experimentation. Nicotin has been isolated from the liver, spleen, kidneys and brain in animals after poisoning with this drug.

Nicotin is not completely excreted as such from the body. It is thought that the chief avenues of escape are by the kidneys, lungs, stomach, saliva and sweat glands.

Lethal Dose.—An exact determination of the lethal dose of nicotin has not been made but it is probably very small. One-half ounce of the leaves, which contain from 1 to 10 per cent of the alkaloid in various types of tobacco, would probably be very toxic if not fatal. Sollmann states that the fatal dose of the alkaloid is about 1 gr. (0.06 gm.). Due to the uncertain alkaloidal content of the infusion, no true estimate of the lethal dose of this preparation can be given. Melsen affirms that in the smoke of ½ ounce of strong tobacco there is sufficient nicotin to prove fatal.

Pathology.—There are no characteristic postmortem findings. There may be hyperemia of the mucous membrane of the gastro-intestinal tract due to the alkaline and therefore mildly caustic nature of the alkaloid. The smoky odor of nicotin is usually detected when the stomach and intestines are examined immediately after death. Cerebral congestion and engorgement of the vessels of the liver, spleen and kidneys are usually observed.

Symptoms.—Nicotin in toxic doses, when no tolerance exists, acts with a rapidity second only to the cyanids. The novice in the use of tobacco can graphically describe the early symptoms of moderate nicotin poisoning. They are salivation, nausea and vomiting, faintness, mental anxiety, frequent voiding of urine, diarrhea and vasomotor instability. When the amount of drug ingested is larger, there is marked physical depression and weakness, the hearing may be dulled and the respiration accelerated. The face is pale and the extremities cold and diarrhea soon develops. Pilcher and Sollmann state that hypertension may exist from the beginning of the toxicosis and persist until death. It is thought that at times the vasomotor centers are paralyzed so that the blood-pressure may at first be very high with a later decrease in tension. That the nutrition of the heart muscle is seriously altered is asserted by Morawitz and Zahn, who state that a constriction of the coronaries takes place with resulting slowed circulation even though hypertension exists in the main arterial system.

A sensation of impending perspiration which does not develop has been described. Disturbances of vision such as amblyopia or even blindness, deafness, photophobia, paralysis of voluntary muscles and extreme prostration do not augur well for a favorable outcome. A rapid depression of all vital functions which manifests itself in a weak thready pulse, gasping or greatly slowed respiration, subnormal temperature and sometimes clonic convulsions are seen before death. On the other hand, death may result almost immediately, as was the case in the poisoning of a relative by the French Count Boscarme, in 1850, in which death followed in thirty seconds. When recovery takes place, health is restored but slowly and the digestive and circulatory organs are prone to disfunction for longer or shorter periods of time.

Diagnosis.—The history and the odor of tobacco are usually sufficient for diagnosis. A record of the consumption of uncertain or questionable beverages, especially in cases where the victim is employed as a gardener or where insecticides are used, should arouse the physician's suspicions as to the possibility of nicotin poisoning. Nicotin in dilutions as high as 1:300,000 will with a 1/10 per cent solution of hydrochloric acid display an opalescence which, on standing, deposits characteristic crystals.[1] The injection of a frog with nicotin results in a characteristic position being assumed with thighs at right angles to the body and the lower half of the leg against the thigh, the feet meeting at the back of the animal. The promptness with which collapse often follows is suggestive of either cyanid or nicotin poisoning.

Prognosis.—The prognosis depends on the form in which the drug was taken and the percentage of the alkaloid contained in the leaves. Tolerance or lack of the same will influence the toxic effect of the drug. Death has occurred in as short a time as thirty seconds and as late as seven hours in acute poisonings.

Preventive Treatment.—If tobacco must be consumed, let it be done by adults who in turn will make it impossible for children to obtain pipes or tobacco in any form as playthings. The use of tobacco as a medicine seems both unnecessary and unwise since the treatment of skin lesions, pruritis and intestinal parasites can be carried out by means of other agents. It would be folly to urge more moderation in the use of the weed from which Raleigh and millions after him have derived solace and companionship. Care in the handling and storing of nicotin insecticides should be urged.

Immediate Treatment.—Due to the prompt action of this poison the following steps should be taken at once:

1. Empty the stomach at once, using warm water as a lavage or, if poisoning has taken place from an enema, give a copious colonic irrigation, using warm water or sodium bicarbonate solution, 5 per cent.

2. The patient should be placed in a recumbent position and plenty of fresh air admitted to the room.

3. If the heart action is depressed, administer strychnin sulphate 1/30 gr. (0.002 gm.), camphor 2 gr. (0.13 gm.), caffein sodium benzoate 1 to 2

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[1] The reader is referred to modern textbooks on physiological chemistry for a detailed description of the steps necessary to arrive at an accurate qualitative and quantitative estimate of nicotin in the body tissues. See also McNally (1920).

gr. (0.064 to 0.13 gm.) under the skin or give alcohol or aromatic spirits of ammonia by mouth.

4. External heat is indicated for the depression. A hot coffee enema is frequently of aid for this purpose.

5. If the respiratory center is depressed, artificial respiration is indicated. Oxygen should be given by inhalation. Agents may be used for reflex stimulation such as brisk rubbing of the extremities, dry heat, the inhalation of aromatic spirits of ammonia, dashing cold water over the head and the use of mild electrical stimulation.

OXALIC ACID

Occurrence.—Oxalic acid is of but little use to the physician as a medicine. It is of interest, however, because it has given rise to serious poisonings and from the standpoint of toxicology is, therefore, the most important of the organic acids. On account of its resemblance oxalic acid has been mistaken for cream of tartar or Epsom salts with grave results. It is used about kitchens as a means of polishing copper kettles or more often perhaps as a bleaching agent. Under the common name of "essential salts of lemon" or "salts of sorrel", the acid potassium oxalate is also used to remove ink stains from the hands or from fabrics. Not infrequently the similarity between the appearance of this active poison and harmless salts has led to grave toxicoses. Oxalic acid occurs in nature rather commonly, being found in rhubarb, cinchona, and sorrel. A recent report appeared in the public press of the poisoning by oxalic acid of a family which partook largely of the roots and leaves of the rhubarb plant. Finally the use of oxalic acid in the dyeing and printing of calico as well as a bleaching agent in the straw-hat industry exposes the workers thus employed to accidental ingestion.

Absorption, Metabolism and Excretion.—Oxalic acid is readily absorbed by the gastro-intestinal mucosa when taken by mouth. It is probably very resistant to oxidization and many writers doubt that any oxalic acid is burned in the human body. Mürset, in 1885, stated that calcium oxalate in the form of rod-shaped crystals may be found in all the organs after large doses have been swallowed.

From 90 to 95 per cent of the oxalic acid taken into the body is excreted by the kidneys. The urine when first passed contains this drug in the form of oxaluric acid. Later decomposition takes place and urea and oxalic acid are split off and finally calcium oxalate, which is an almost insoluble salt, is formed. The envelope-shaped crystals of this salt when found in the urine are valuable as a diagnostic aid in determining whether poisoning has taken place. The kidney tubules are sometimes blocked with these crystals and when found postmortem they point toward the cause of death.

Pathology.—The findings at the postmortem examination of patients dying from poisoning by this drug are not characteristic. There may be white burns on the lips and buccal mucosa; again these eschars may be yellow or brown in color as a result of staining by blood or bile respectively. The gastric mucous membrane is not usually corroded but is often hyperemic. Sometimes calcium oxalate is deposited in the lining of the stomach as white opaque plaques. Rarely perforation of this viscus occurs. The kidney is hyperemic and the tubules may be loaded with the crystals of the insoluble oxalate of calcium.

Fatal Dose.—The smallest amount of this drug known to have caused death is 1 dram (4 gm.) although the usual fatal dose is several times this amount. Recovery has occurred after 2 ounces (60 gm.) have been taken.

Symptoms.—The symptoms which are observed after the ingestion of oxalic acid are those which arise as a result of a caustic effect on the oral and pharyngeal lining in addition to those caused by a systemic poison. The attention of the victim may first be directed to the fact that some unusual substance has been swallowed by the bitter hot taste of the mixture. There is burning and a sense of constriction in the throat and esophagus and finally acute gastric pain is experienced. Nausea and vomiting are not long delayed, the vomitus consisting of a dark-colored, highly acid material which may be streaked with bright blood. The emesis is prolonged, violent and very exhausting to the patient. The progress of the symptoms may be very rapid, the circulatory system quickly showing a great depression, the general prostration deepening until early dissolution during a convulsion takes place. On the other hand, the gastro-intestinal symptoms may remain comparatively inconspicuous and the nervous picture largely predominate. Often what appears to be a violent stimulation of the whole central nervous system is observed at first. Later incoördinate movements, twitching of the facial muscles, formication on the trunk and extremities, numbness of the finger tips and paralyses more or less general in extent appear. This loss of power is thought to be due to a generalized precipitation of nerve tissue calcium as a result of its union with the oxalic radical, thus forming calcium oxalate. Both tonic and clonic convulsions have been observed. Frequently the pulse is small, compressible and irregular. The body is cold and cyanosis of the lips and extremities as a result of circulatory depression is seen.

Glycosuria and albuminuria with the presence of numerous tube casts are rather constant urinary findings. It is thought that the presence of sugar in the urine can be explained by the fact that the metabolic processes are much hindered by the presence of oxalic acid in the body. Calcium oxalate crystals are sometimes found in the urine after poisoning with oxalic acid. Nephritis of a serious grade is not a common complication. The respiratory quotient falls since the production of carbonic acid is greatly diminished.

In fatal cases death results from palsy of the respiratory center and usually occurs more rapidly than from many of the other caustic agents. Instances have been seen in which the patient fell unconscious immediately after the poisoning and death occurred without the stupor lessening.

When death does not take place as a result of the acute toxicosis, distressing nervous and metabolic sequelæ may occur. Among these conditions may be mentioned neuralgias, asthenia, melancholia, asthma, eczema, prurigo and demineralization of the bones as a result of the withdrawal of the calcium. Not infrequently calcium oxalate is deposited in the joint structures and gives rise to the so-called oxalic gout.

Diagnosis.—Sometimes the patient will be able to state the nature of the substance taken as soon as he realizes that a mistake has been made. On other occasions the cause of the trouble is not so easily ascertained. The local signs with the frequent rapid development of grave symptoms as well as the urinary findings usually give some clue as to the nature of the ailment. Five drops (0.3 mil) of a saturated solution of sodium hypochlorite with 2½ drams (10 mils of urine and 5 drops (0.3 mil) of a 10 per cent solution of magnesium sulphate will give rise to a pink tint in the presence of oxalic acid.

Prognosis.—When a lethal amount of this poison has been swallowed, death may be very prompt. Indeed, a case has been reported in which death took place in ten minutes after poisoning. Several hours may elapse without grave signs developing and yet sudden fatal collapse take place.

Preventive Treatment.—No poison should be placed near where food is being prepared and, if cleaning or scouring materials of a toxic nature must be kept in the kitchen, the container should be distinctive either in color, size or shape. The same precaution would apply on a larger scale to the industries using this drug. The purchase of a new straw hat would appear to be a good preventive measure if the bleaching solution required to make the old one presentable is likely to gain entrance to the body.

Immediate Treatment.—Fortunately there is always handy in some form a very powerful and efficient antidote for oxalic acid. Calcium in any form is highly efficacious. The stomach should be immediately emptied by lavage, a calcium solution being used if immediately obtainable. After emptying the stomach, calcium salts should be given in generous amounts. This antidote may be given as the chlorid, as the lactate, as common chalk or as limewater in large quantities. The ingenuity of those near will suggest the removal of whitewash from a wall, the ceiling or a fence and after rubbing up with water the administration of this solution in large quantities. Calcium salts in the presence of oxalic acid will form the very insoluble calcium oxalate. One pint (500 mils) of a solution of 1 per cent sodium bicarbonate and 0.25 per cent calcium chlorid may be given intravenously where haste is indicated. Calcium lactate is a good drug for intravenous use. Water in large amounts should be administered to prevent the clogging of the renal tubules with oxalate crystals. A saline cathartic, preferably magnesium sulphate, in 3 to 4-ounce (90 to 120 mils) doses should be given.

General Treatment.—Support of the embarrassed heart is usually necessary, caffein and digitalis being useful for this purpose. External heat and enemata of strong coffee are but two of the supportive measures which will suggest themselves as useful in relieving the shock incident to the swallowing of large doses of this poison. The diet should be liquid until the acute stage is past.

ALKALIS AND ACIDS

Sodium hydroxid, $NaOH$.
Potassium hydroxid, KOH.
Calcium oxid (Quicklime) CaO.
Sulphuric acid, H_2SO_4.
Nitric acid, HNO_3.
Hydrochloric acid (Muriatic acid) HCl.

Occurrence.—The caustics destroy life by causing the death of the tissues with which they come in contact. They may accomplish this result by acting as a protoplasmic precipitant, by charring or consuming the tissues or by causing such an active inflammation that extensive necrosis finally takes place. These substances are rarely used for homicidal purposes because of the relative ease with which members of this group of drugs are recognized. The suicide infrequently chooses these agents to accomplish his purpose because of the common knowledge of the pain incident to their ingestion. Occasionally the caustics are taken in mistake for harmless medicines with grave results. Household lye which is commonly used for cleaning purposes is frequently so carelessly stored about the house that children are exposed to the danger of poisoning from this source.[2] Nitric acid fumes have been responsible for many accidental deaths. Carboys of this acid are sometimes spilled in the holds of cargo vessels or other closed spaces and workmen entering to repair the damage are quickly overcome.

Absorption, Metabolism and Excretion.—The effects of the general absorption in poisoning with the caustics are of relatively minor import, the essential harmful results arising from the direct contact of the chemical with the skin or mucous membranes. The alkalis unite with the tissue elements to form alkaline albuminates or with fats to form soaps. The alkalis in particular have the ability to invade the tissues deeply and for this reason their action is very painful and the scars which result are extensive and give rise to troublesome secondary contractions. Both the acids and alkalis are very hygroscopic and by withdrawing water from the tissues favor or aid in bringing about their death. It is likely in the case of the acids that some general absorption takes place although the chief action is local. Excretion is probably largely by way of the kidneys and the intestines.

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[2] The common household cleansing powders contain sufficient free alkali to poison children who consume them through ignorance. There should be state laws requiring that these substances be branded as poisonous.—Editor.

Pathology.—Extensive necroses and sloughing are the chief pathologic changes seen in poisoning with these caustic substances. There is usually evidence of a marked corrosive action on the lips, mouth and pharynx in acid poisoning. Especially is this true in the upper and lower esophageal segments. The mucous membrane of the esophagus is sometimes seen to hang in long necrotic shreds. After the swallowing of sulphuric acid the lips may be brown or even black in color, the tongue covered with a white, grayish or brown layer of charred tissue. Dark streaks or spots may be present about the face or on the neck where the acid has been accidentally spilled at the time of ingestion. The alimentary canal shows a general hyperemia. The corrosion of the gastric mucosa is seen especially at the pylorus, because of the tendency of the caustic to accumulate at this site. The acids usually give the blood a deep dark color due to the change of the hemoglobin to acid hematin. Nitric acid is an exception to this statement, a yellowish color usually resulting. Perforation of the stomach, especially after the ingestion of sulphuric and nitric acids, has been reported. In poisoning with hydrochloric acid stricture of the esophagus is perhaps more frequent than in burns with either sulphuric or nitric acid while perforation of the stomach occurs less frequently. In poisoning by alkalis there is often observed an edematous swelling of the epithelium which tends to separate and expose the underlying reddened and inflamed tissues. The corrosive effects of alkalis on the alimentary tract are similar to those resulting from acid poisoning. Scar formation following ingestion of alkalis is more extensive than that resulting from acid poisoning, while esophageal stricture is a common secondary occurrence.

Fatal Dose.—There is a wide variance of opinion in the literature as regards the fatal dose and rapidity of action of the caustics. One fluid dram (4 mils) of sulphuric acid has caused death in an adult and probably one-half this quantity would be fatal to an infant. Two drams (8 mils) of the concentrated nitric acid have destroyed life in the adult. Death usually occurs in from twenty-four to forty-eight hours after swallowing nitric acid, although death has occurred more promptly after the fumes have been inhaled. Four drams (16 mils) of hydrochloric acid would be fatal to an adult. One dram (4 mils) has produced death in a child. The fatal period varies from a few hours to several months. It is not possible to state accurately the fatal dose in the case of the alkalis, although caustic alkalis are generally less active than caustic acids.

Symptoms.—The symptoms arising in each case from ingestion of members of the caustic group are similar and will therefore be discussed collectively. The extent of the damage and the consequent symptom picture depend largely upon the concentration of the acid or alkali, the time during which it acts before treatment is instituted and the extent of the surface with which it comes in contact. If taken into the gastro-intestinal tract the patient first complains of burning pain in the mouth and throat and difficulty in swallowing. Nausea and vomiting soon take place, the vomitus being often stained with bright blood or, in acid poisoning, it may be dark in color as a result of the formation of acid hematin. Later the vomitus contains shreds of detached mucous membrane which at times may assume considerable size. Dysphonia is often present and intense thirst exists. The objective symptoms relative to the pharynx have been described under the section on pathology. Not infrequently, when a suicidal attempt to swallow concentrated sulphuric acid has been made, a spasm of the pharynx prevents the passage of the acid into the stomach and the fluid is regurgitated, burning the tissues about the angles of the mouth and about the neck. There is often diarrhea, the dejections containing macroscopic blood; or, on the other hand, constipation may be present. As a result of the violent impression of caustics on the gastro-intestinal tract, the abdomen is frequently greatly distended and extremely tender to palpation. When perforation of the stomach occurs the symptoms of peritonitis are added to the already distressing picture.

If the contact with the tissues has been widespread and extensive destruction has taken place, the patient may display marked evidence of shock from this cause. The stagnation of blood in the splanchnic area with a consequent anemia in the brain and other vital centers is an additional factor in producing this condition. As a result vertigo, delirium, convulsions, collapse and coma may be observed and death may take place before the local symptoms have had sufficient time to develop.

The pulse may be small and accelerated or, due to vagus stimulation, may not be increased in rate. Due to parenchymatous changes in the kidney the urine is usually diminished in amount and contains casts, albumin and red blood-cells. Fever is usually present when sufficient time has elapsed for absorption of the toxic necrotic substances, although when shock is present the temperature is subnormal.

If the fumes of nitric acid have been inhaled, conjunctivitis, bronchitis, pulmonary edema or pneumonia are likely to be observed. Death has taken place promptly as a result of spasm or edema of the glottis when the fumes of nitric, or more rarely hydrochloric acid, have been inspired. Due to the damage which has been inflicted upon the esophagus and stomach, recovery takes place slowly, nutrition suffers and the body strength is regained with difficulty. Esophageal strictures and contractures only serve to make a miserable condition more distressing.

Diagnosis.—It is not difficult to arrive at a diagnosis when corrosives have been swallowed. The exact acid or alkali taken is somewhat more uncertain. The alkalis are likely to give rise to a slimy slough, gelatinous in appearance and of greater depth than in the case of the acids. The characteristic tissue changes in sulphuric, nitric and hydrochloric acids have been described. The yellow xanthoproteic reaction seen in a nitric acid burn may be confused with a picric acid stain, but in the former the application of alkalis changes the color to orange, while no such effect is seen in the latter.

Prognosis.—Death may result promptly from shock or edema of the larynx although the fatal period may be greatly delayed. If the patient survives the acute symptoms, death from gastric ulceration and slow perforation or even from actual starvation as a result of cicatricial stenotic contractions or extensive destruction of the gastric mucous membrane may follow.

Immediate Treatment.—The physician should bend every effort to dilute the caustic substance, for it is not the total amount of the acid or alkali ingested which is likely to do the greatest harm, but it is the concentrated substance which does the damage. To this end the patient should be required to drink water in abundance. If the case is seen very early or the escharotic effect of the poison is not intense, the stomach tube may be used. The passing of a tube in all cases is not devoid of danger and is frequently definitely contra-indicated. Demulcent and protein drinks are useful and of these groups boiled starch, slippery elm infusion, acacia, white of egg or milk are useful. The exhibition of morphin is usually required to control the agonizing pain.

Chemical Antidotes.—In acid poisoning the alkalis are chemically antidotal, magnesium oxid being particularly useful. Care should be exercised in administering the carbonates, since there is some danger of rupturing an eroded stomach by the generation of carbon dioxid gas and the consequent overdistension of this viscus. The free alkalis are too caustic and the potassium compounds are objectionable because of the danger of toxic absorption. When the emergency is grave, any alkali should be used, even chalk or the whitewash from the wall, but diluents are preferable to chemical antidotes paid for in valuable time.

In alkali poisoning the acids are to be used. Vinegar or lemon juice is useful and usually to be quickly procured. If these remedies are not available, any acid in 1 per cent strength may be used in the emergency. Feeding by rectum is usually necessary and supportive measures are indicated in the majority of cases. Fluid by vein or under the skin is required for the collapse and dehydration. A 1 per cent solution of sodium bicarbonate will meet this indication.

CARBON MONOXID

(Carbonic Oxid, Illuminating Gas, CO)

Occurrence.—Carbon monoxid is a colorless, practically odorless gas produced in large quantities as a product of the incomplete combustion of coal or other carbonaceous matter. With an excess of oxygen, burning is complete and carbon dioxid alone is produced; with the progressive limitation of air or oxygen the amount of carbon monoxid produced increases proportionately. Ordinary illuminating gas consists chiefly of hydrogen, hydrocarbons and carbon monoxid. Coal gas, produced by the destructive distillation of coal or coke, contains from 4 to 10 per cent of carbon monoxid; water gas, prepared by the passage of steam over white hot coke or anthracite, contains 30 to 40 per cent of this poisonous gas. A concentration of less than ½ per cent in the atmosphere breathed is adequate to produce serious if not fatal poisoning.

Accidental and suicidal poisoning by carbon monoxid are of frequent and common occurrence. Stevens states that this gas is responsible for more deaths than all the other gases combined.

Poisoning with carbon monoxid occurs from inhaling the smoke of burning buildings, after mine explosions, from the fumes of damped furnaces and stoves, in the "after-damp" of old wells, from the exhaust (4 to 12 per cent CO) of the engines of automobiles running in a closed or poorly ventilated garage, and from the accidental or intentional inhalation of illuminating gas. Accidental poisonings are reported as a result of the use of household appliances for cooking and heating, especially where the ventilation is insufficient, and from gasoline-driven motor boats with enclosed cabins. Eighty miners lost their lives recently at Spangler, Pennsylvania, as a result of inhaling fire damp, which contains a high percentage of carbon monoxid. In Philadelphia, during the years from 1910 to 1921 inclusive, 1,429 cases of suicide by drugs including illuminating gas were recorded of which number 962 or 67.3 per cent chose illuminating gas as the sure and convenient way to euthanasia.

Absorption, Metabolism and Excretion.—Absorption is prompt. Carbon monoxid is readily absorbed through the endothelial lining of the pulmonary alveoli, the rate of absorption being roughly proportional to the concentration of the gas in the inspired air.

Carbon monoxid unites with the hemoglobin of the red blood-corpuscles evidently at the same site or bond of union in the hemoglobin unit as the combinations with oxygen take place. The carbon-monoxid hemoglobin or carbonyl-hemoglobin thus formed is a stable compound, the affinity between the carbon monoxid and hemoglobin being about two hundred and fifty times as great as that existing between oxygen and hemoglobin in the analogous oxyhemoglobin combination. As a result the oxygen is displaced and the place in the hemoglobin structure normally occupied by oxygen is now occupied by the carbon monoxid unit. Thus the oxygen-carrying function of the hemoglobin is abolished, and the red corpuscles no longer serve to carry oxygen from the lungs to the tissues. The extent of the resulting asphyxia will depend upon the amount of carbon monoxid absorbed and the number of erythrocytes saturated by this gas.

Excretion of carbon monoxid is favored by the removal of carbon monoxid from the inspired air and the increase in concentration of the oxygen in the respiratory alveoli. Most of the carbon monoxid passes from the corpuscles and plasma into the pulmonary alveoli and is discharged in the expired air. A small part is excreted unchanged by the kidneys. Carbon monoxid is not oxidized to carbon dioxid in the body.

Pathology.—The appearance of the body after poisoning by this gas is characteristic. It is not unusual in cases where accidental or suicidal death has resulted from the inhalation of illuminating gas to discover the body lying in bed with the rosy hue of health on the cheeks but with a cherry-red tongue and lips. Cyanosis is usually absent and the skin is frequently pink or pale in color. The face may be injected, the eyes bright and staring. Sometimes there is a delayed rigor mortis, the limbs being supple, while in other instances postmortem rigidity seems to be hastened. Large rosy-colored areas are frequently seen over the chest, abdomen and thighs. Abdominal incision discloses arteries which are full of bright red fluid blood, the viscera, fatty and muscular tissues being of the same rose red color. A bright red fluid blood is of the highest diagnostic value. Pneumonitis with edema is not infrequently seen and a pseudomembranous exudate on the gingival surfaces, trachea, colon and rectum has been reported. Gangrene of the muscles of the neck has occurred in rare instances. Deep bed-sores have been known to form in a very short time.

Generally speaking, the most constant pathologic changes in carbon monoxid poisoning consist of a general hyperemia with scattered small hemorrhages in all organs and parenchymatous fatty degenerative changes in the liver, kidneys and muscles.

Fatal Dose.—In 1881, Gruber found that a concentration of 0.024 per cent of carbon monoxid in the air was harmless even after inhalation for several hours. The threshold of toxicity probably begins at 0.05 per cent concentration, is severe at 0.07 per cent, dangerous at 0.16 per cent and generally fatal from 0.2 to 0.4 per cent (Sollmann).

Symptoms.—Generally speaking the symptoms of carbonic oxid poisoning are those which are to be expected when the normal tissue metabolism is halted or delayed as a result of a deficiency or loss of oxygen. Carbon monoxid has little if any inherent toxic action and acts only as a barrier or block to the normal oxygen-carrying function of the red cells. Haggard's statement of the physiology of this asphyxia gives a plausible explanation and deserves mention. He states that, as a result of the anoxemia, the respiratory rate is increased with a resulting diminution of blood carbon dioxid, thereby eliminating the source of respiratory center stimulation. Respiratory death is a natural sequence of anoxemia and a further result is the development of heart block in its various stages.

The onset is insidious at times, there being no prodromal symptoms of any definite sort. The patient becomes suddenly dull or stuporous before he or his companions have any knowledge that a poisonous gas is being inhaled. Usually there is an early sense of pressure on the temples, tinnitus aurium, throbbing of the vessels, malaise, disturbed vision and mental excitement or delirium followed by nausea and vomiting and a sense of muscular weakness. The early symptoms, which represent an initial cerebral stimulation, are followed by a corresponding depression. The pulse is slowed from vagus stimulation or impairment of auriculoventricular conduction and, though the blood-pressure is at first elevated as a result of stimulation of the vasoconstrictor center, later hypotension is seen as vascular tension and myocardial integrity are lessened.

Mental dulness, increasing to stupor or deepest coma, great prostration, thready pulse, hypotension, slow shallow respiration are symptoms which later present themselves. Muscular twitchings and convulsions are not infrequently observed, the latter being of the epileptiform type. Respiration of the Cheyne-Stokes' type, relaxation of the sphincters and deepening of coma with hyperpyrexia are signs of the gravest significance. Respiratory failure is usually the cause of death, the heart continuing to beat after respiration has ceased.

Albuminuria is observed in 20 per cent of the cases and in about 70 per cent of carbon monoxid poisonings a reducing substance is found in the urine, which some observers report to be dextrose while others have isolated glycuronic acid. In doubtful cases this action on Fehling's solution may be useful to confirm the diagnosis. Lactic acid appears in the urine in cases of severe poisoning. A leukocytosis is often noted.

Sequelæ.—Even days or weeks after the acute symptoms have subsided and recovery seems assured, grave sequelæ are frequently observed. These may range in severity from persistent headaches, palpitation, local hyperemias, gastro-intestinal disturbance, localized edema, dermatitis and transient glycosuria to paralysis of central and peripheral nerve tissues, gangrene of the hands and feet, mental disturbances, amnesia, choreiform movements, cardiac weakness and various psychoses of a lasting character.

Abt and Witt report a case of carbon monoxid poisoning in a child five years of age in which total blindness remained as a sequela. These writers state that many serious optic sequelæ may be seen following poisoning by carbonic oxid.

McConnell and Spiller and also Hill and Semerak call attention to the fact that carbon monoxid is capable of causing fatty degeneration of the intima and muscle coats of vessels with resulting bilateral softening of the lenticular nuclei.

Aspiration pneumonia as a result of inhalation of infectious particles during the period of unconsciousness is occasionally observed. Even after consciousness has been restored, pulmonary edema and pneumonia are possibilities which the physician should bear in mind.

Frequent mention is made in medical literature of localized gangrenous conditions following poisoning by carbon monoxid. This is explained by the loss of the blood of oxygen-carrying power resulting in consequent tissue death.

General Treatment.—Prophylactic treatment is not always possible. Since carbon monoxid gas is odorless, the unfortunate individual inhaling it is not warned of its presence by the sense of smell. Fortunately sulphur compounds are frequently admixed and the presence of a deadly poison is sometimes announced by these comparatively harmless gases. Filtration of gases through the soil may remove the sulphur compounds so that even this safeguard is not availing. It has been suggested that white mice, which are affected from twelve to twenty minutes earlier than is man by this gas, be used to test mine air for the presence of carbon monoxid. It is to be remembered that the specific gravity of carbon monoxid is only .967 and that therefore the spaces near the ceilings of rooms and the roofs of mines are likely to contain the greatest concentration of deadly gas. Ventilation in mines and boiler rooms, attention to plumbing, the wearing of oxygen masks, the discarding by firemen of any reliance on the gas mask used by soldiers in the recent war, all should commend themselves as sensible precautions. Automobile engines should never be started in closed garages.

The United States Bureau of Mines recommends the preparation and constant availability of tanks containing oxygen to which 8 to 10 per cent of carbon dioxid is added. Masks suitable for the administration of this mixture should be attached.

Immediate Treatment.—Remove the patient from the contaminated atmosphere at once. Every minute counts, for it is to be borne in mind that every second of complete asphyxia makes recovery more doubtful. If natural respiration has ceased, artificial breathing or forced inhalation of oxygen must be begun as soon as an oxygen tank can be procured. Every hospital ambulance and first-aid station should be abundantly supplied at all times with oxygen. Venesection with transfusion of healthy blood, if employed within the first two hours after poisoning, seems to have given good results. In the presence of an excess of oxygen, the carbon monoxid hemoglobin is again decomposed and the active elimination of carbon monoxid is begun. This decomposition is said to take place in the first hour of oxygen treatment and, if some favorable response is not noted at the end of this period and coma continues, some definite injury to nerve centers as a result of the anoxemia has probably taken place. Alkalis are indicated for the acidosis. Haggard and Henderson claim beneficial results from the exhibition of oxygen with 8 per cent of carbon dioxid, the carbon dioxid augmenting respiration and the increase of oxygen thus inhaled hastening the elimination of the carbon monoxid. It is to be remembered that treatment to be of avail must be prompt, that the life of the patient is ofttimes saved or lost in the first hour, and that blood or saline transfusion after venesection or the exhibition of oxygen are of little use if two hours have passed without treatment being instituted.

Symptomatic treatment should also be employed both in regard to immediate and late symptoms. Care should be taken not to expose the patient to the cold; liquids should be supplied in adequate amounts either by hypodermoclysis or enteroclysis. Respiratory and cardiac stimulants are indicated.

Hydrogen dioxid administered per orem or hypodermically has its advocates but adequate proof of its efficacy seems to be lacking.

Diagnosis.—This is rarely a difficult problem. The history of the onset, the symptoms of asphyxia without cyanosis, the cherry-red appearance of the skin, all point out to the physician the proper solution. The spectroscope is of the highest utility in detecting the presence of carbon monoxid hemoglobin in the blood.

Prognosis.—The outlook for recovery depends on the duration of the exposure and the concentration of the carbonic oxid in the inhaled air. Stevens states that if the patient has inhaled a 0.2 per cent concentration of carbon monoxid with air for four or five hours, or a 0.4 per cent for one hour, death may be expected. When a 2 to 5 per cent concentration of carbon monoxid has been inhaled, almost all of the oxygen-carrying power of the red corpuscles is immediately destroyed and death occurs about as rapidly as in drowning. This is the case when illuminating gas with only slight admixture of air is inhaled.

If the coma has lasted longer than thirty-six hours the chances for recovery are remote. If edema or cutaneous blebs appear the prognosis is unfavorable. If the acute effects have largely disappeared in from three to four hours the prospects for recovery are good.

ABORTIFACIENTS

Occurrence.—Almost from the very beginnings of civilization attempts have been made to interfere with the natural biologic sequence of the human reproductive cycle. The problems involved in the production of abortion and the motives which actuate the attempt are so deeply interwoven with the civilization, the morals and the economics of nations that to discuss the subject exhaustively from the standpoint of etiology would require more space than can be given to this article. Moreover, the average status of the general public morals varies in different countries and constitutes an important influence. The incidence of criminal abortion cannot be definitely stated, much less the frequency of abortions and poisonings through the use of abortifacients, since only in those cases where life has been jeopardized or actually lost do the details come to light or find a place in the report of the case. The production of abortion by means of mechanical agents does not concern us in this chapter.

To enumerate the members of that great class of drugs which have been employed in the attempt to terminate pregnancy would require a presentation of almost the whole list of official drugs with the addition of many which have little or no medicinal use and in truth frequently only a fancied action on the pregnant uterus. Davis states that 57 drugs reputed to have abortifacient properties are mentioned in various works on materia medica. Every country and clime has its favorite abortifacient drugs and these are frequently influenced if not wholly determined by the flora of the particular locality. The frequent use of the extract of cotton-root bark (ext. gossypii radicis cortex) by the negroes of the southern states serves as a good example of this geographical influence. Indeed so varied is this local effect that there seems to be even an industrial aspect to the problem. The frequency of the use of phosphorus in Sweden as an agent to empty the uterus no doubt has some relationship to the match industry in that country.[3] Lewin in an exhaustive volume on the drug abortifacients has given some interesting information concerning the favorite agents of many countries. In France savin (sabina), arbor vitæ (thuja), and rue (ruta); in England pennyroyal (Hedeoma pulegioides), diachylon pill and white hellebore (veratrum viride); in Germany savin, aloes, coffee, vinegar, balsam of Peru and borax; in Austria savin; in Sweden phosphorus; in Turkey aloes and savin; in Greece opium and belladonna; in Russia savin and mercuric chlorid; in Japan musk and the root of Achyranthes aspera Thumb.; in China musk; and in the United States ergot, savin, tansy (Tanacetum vulgare), pennyroyal, cedar oil, nutmeg and cotton-root bark are used. It will be quickly observed from the above statement that the preparations derived from the vegetable kingdom preponderate. The influence of the folk lore of a people and the discussion among women of the efficacy of any of the vegetable or mineral drugs plays not a negligible rôle in the abortifacient drug incidence.

It has been stated by Meyer that there is 1 abortion to every 1.7 to 2.3 pregnancies, while Robinson believes that there is 1 criminal abortion to every 2.4 births. The writer is unable to cite authenticated statistics as to the relative frequency of mechanical and drug abortions but he believes that the former are in the great majority. The chief purpose of this article is to endeavor to set forth not the success with which either of these illegal measures are employed but to enumerate the usual symptoms and describe the common pathologic changes which follow the toxic ingestion or use per vaginam of drugs with the intention of emptying the uterus whether this result does or does not follow. What is said in regard to poisonings by the use of these drugs as abortifacients applies in general equally as well to these same drugs when used as contraceptives.

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[3] Lewin states that out of 1896 poisonings with phosphorus occurring between 1873 and 1892, 616 were the result of attempted abortion.—Editor.

General Considerations.—All drugs which have any abortifacient properties act in one of three ways:

1. By a general systemic poisoning effect.
2. By acting locally and specifically upon the uterine musculature.
3. By acting secondarily on the uterus through their effect on the gastro-intestinal and genito-urinary tracts.

It will be at once observed that, in the first and last general classes particularly, grave damage may be done to the patient and her life placed in danger without affecting the uterus at all. In fact, the literature repeatedly describes cases in which the life of the unwilling mother was sacrificed without the uterus being emptied and without any signs of a threatened abortion manifesting themselves. In the second group which represents the smallest number of drugs, there is somewhat less danger of damage being done to the extrapelvic vital structures.

Classification of Drugs Employed as Abortifacients.—It seems to be a logical plan of procedure to endeavor now to classify the most important abortifacient drugs from the standpoint of toxicity and frequency of use. The writer uses the term "abortifacient" not in the sense of implying that the drugs actually produce abortion but that they are used with this object in view.

I. The Irritants.
  A. The Irritant and Toxic Volatile Oils.
    Savin (sabina), arbor vitæ (thuja), tansy (tanacetum vulgare), nutmeg, rue (ruta), pennyroyal (Hedeoma pulegioides), turpentine, sassafras and thyme.
  B. The Drastic Purgatives.
    Croton oil, colocynth and jalap.
  C. Intestinal and Renal Irritants.
    Capsicum, cantharides, mustard, cedar oil, and balsam of Peru.
  D. The Simple Purgatives.
    Aloes.
II. The Ecbolics (Greek-expulsion).
  A. Ergot, cotton-root bark and black snake root.

III. Caustic and General Protoplasmic Poisons.
  A. Acids.
    Sulphuric, hydrochloric, nitric, acetic, oxalic, carbolic and carbonic acids.
  B. Metals and Inorganic Salts.
    Phosphorus, mercuric chlorid, arsenic, potassium cyanid, borax, antimony, potassium chlorate, iodids, nitrates, permanganates, chromates, alum, ferric sulphate and other iron preparations.
  C. Gases.
    Carbonic oxid and carbon dioxid.
  D. Organic Substances.
    Alcohol, chloroform, nitrobenzol and anilin.

Having thus laid the foundation we will now proceed to a more detailed discussion of the toxic effects of these drugs with some elaboration on diagnosis and treatment.

IRRITANTS

Occurrence and Mode of Action.—This is probably the most commonly used group of abortifacients. Not only have the members of this group acquired somewhat of a reputation with the laity as effective and harmless agents to produce abortion, but they are also in a large measure easily available and sold under common popular trade names. When the emptying of the uterus does actually take place as a result of the use of these drugs, the effect is the result of a marked active congestion of the pelvic organs which accompanies or follows an irritative congestion of the gastro-intestinal and genito-urinary tracts. They have no direct action on either the musculature or the lining of the uterus.

Absorption, Metabolism and Excretion.—The drugs represented by this group are not quickly absorbed to any marked degree but exert their chief action locally, although there may be a gradual absorption if these agents remain long in the gastro-intestinal canal. A number of these drugs, however, enter the blood-stream and are eliminated by the kidneys, this applying especially to the group of irritant and toxic volatile oils.

Pathology.—The postmortem findings when death has occurred as a result of the toxic ingestion of the irritants consist largely of an intense congestion of the gastro-intestinal tract. Ecchymoses may be observed in the wall of the alimentary canal. The kidneys are usually the seat of an acute inflammation. The pelvic organs are swollen and congested. The uterus often fails to evacuate its contents.

General Symptoms.—The symptoms incident to toxic use of this class of drugs are chiefly those of a violent gastro-enteritis. There is usually obstinate nausea and vomiting and diarrhea is constantly seen. Due to the stasis of blood in the splanchnic area symptoms attributable to anemia of the vital nerve centers arise. Anxiety, vertigo, delirium, convulsions and coma are often observed. There is symptomatic evidence of an active hyperemia of all the abdominal viscera and, if an ecbolic effect is at all manifested, it is seen partly because the uterus is one of the organs which share in this secondary congestion and in part because the violent vomiting and purging and straining so irritates the uterus that contractions may set in and evacuation result.

Special Symptoms—*Savin* (*Sabina*).—This drug may well be taken as a type of the irritant, toxic and ecbolic volatile oils. It is one of the most popular and generally used drugs of this group or even of this whole class of irritants and is used in practically all countries. The infusion or decoction of Juniperus sabina contains pinene, cadinene and sabinol which are volatile oils similar to turpentine in composition and irritant action but are even much more toxic. The oils of savin cause vesiculation when applied to the unprotected skin. Toxic symptoms consist of salivation, nausea, vomiting, abdominal cramps and diarrhea. There may be hematuria and dysuria. Lewin states that six drops have caused toxic effects. Hemorrhage from the nose, lungs and intestines has been described but bleeding from the genito-urinary tract is more common. In order to produce any abortive effect, drugs of this group must be given in such large quantities that life itself is endangered. The respiratory rate may be accelerated at first, but later becomes slowed, labored and extremely difficult. Arbor vitæ and tansy both contain thujol, a toxic and irritant volatile oil. A teaspoonful of the volatile oil of tansy has caused dangerous symptoms. Pennyroyal is probably the least irritant of this group, although a teaspoonful of its volatile oil has produced grave poisoning. Macht reports the death of a girl, sixteen years of age, as a result of swallowing thirty-six pennyroyal pills of a well-known brand. Myristicene is the active principle of nutmeg and is a volatile oil. Poisoning has occurred as a result of eating one and one-half nutmegs. Nutmegs are not unpopular as a type of abortifacient, being usually crushed or grated, mixed with water and swallowed.

Drastic Purgatives.—Drastic purgatives in massive doses produce violent purging and tenesmus. Glaister reports a case in which a dram (4 mils) of croton oil was given by mistake. Sweating, purging and collapse followed but recovery took place. Brief mention of these agents is sufficient to suggest to the reader the symptoms and treatment when excessive doses have been taken.

Intestinal and Renal Irritants.—The most important member of this group is cantharides and it may be taken as a type from the standpoint of toxic symptoms. The only possible ecbolic action of these agents is secondary to the violent irritation of the intestinal and genito-urinary tracts. These drugs are largely eliminated by the kidneys and to a less degree by the intestines and, as a result of their irritant action, produce active congestion of the kidneys, the pelvic organs being secondarily effected by the increase in blood supply. Frequently a true nephritis results with the usual symptomatic picture of kidney insufficiency. When cantharides is taken by mouth, thirst, dysphagia, swelling of the tongue and throat, salivation, nausea and bloody diarrhea result. The patient also complains of burning in the urethra, frequent urination and pain in the lumbar region. Casts, albumin and blood appear in the urine. Collapse of the circulatory apparatus is sometimes seen. Twenty-five gr. 1.6 gm.) of the powder and 1 ounce (30 mils) of the tincture has produced death. Coma and convulsions may precede dissolution. The finding of remnants of the shining elytra or wing cases of the insects in the vomitus or stools makes certain the cause of the symptoms and the diagnosis is evident.

Simple Purgatives.—The most important member of this group is aloes which is usually classed as a simple or non-drastic purgative. This drug is believed by many to produce congestion of the pelvic organs and has thus gained some popularity as an ingredient of various abortifacient mixtures. Cushny believes that aloes exerts some direct action on the muscular structure of the uterus itself. In toxic doses given to animals aloes produces a nephritis which affects the epithelium of the tubules chiefly. The urine may be increased or diminished in amount and contains leukocytes, casts and sometimes blood.

Treatment.—The immediate treatment after any of the irritant group has been swallowed should concern itself first with the removal of the offending substance from the gastro-intestinal tract. The use of the stomach tube is at once indicated and large quantities of warm water should be used as a diluent and medium of lavage. Morphin is usually required for the pain. When shock is present, hot coffee by rectum, dry heat and intravenous injection of saline solution are useful. The congestion and irritation of the gastro-intestinal and urinary tracts may be favorably affected by the administration of demulcent drinks such as barley water, acacia, slippery elm and milk in generous quantities. A starch water enema may serve to allay irritation of the lower bowel. The nephritis which often follows the excretion of kidney irritants requires a bland diet and excess of liquids to dilute the urine and cleanse the tubules of the irritant substance. Bismuth and occasionally opiates are useful to control the tenesmus and diarrhea after the intestinal tract has been cleansed of the irritating substance by means of a saline.

The Ecbolics

Occurrence.—The important ecbolics which are used in an attempt to produce abortion are but three in number, ergot being the best known and therefore the most frequently employed. Cushny states that pilocarpin, quinin hydrochlorid and aloes like ergot stimulate contraction of the uterine musculature. This action is in no way comparable to ergot in degree of intensity, and in the case of quinin, at least, Bastedo states that there is certainly an irritant gastro-intestinal effect which may be partly explanatory for any ecbolic result which may be correctly assigned to this drug. Animal experiments have shown that, although ergot does produce powerful contractions of the uterine muscles late in pregnancy, the reputed efficiency of this drug as an ecbolic in the earlier months of pregnancy cannot be demonstrated. This fact nevertheless does not decrease its popular use for this purpose or serve to diminish the poisonings which arise from its ingestion.

Pathology.—Few cases of fatal acute poisonings from ergot are to be found in the literature. Gangrene of the distal phalanges has been produced and a congestion of the mucous membranes of the intestine has been observed. The skin may be jaundiced and extravasations of blood have been observed in the stomach, liver and kidneys.

Symptoms.—Bastedo states that the symptoms of acute ergotism may be divided into those incident to an acute gastro-enteritis and to various nervous manifestations. When ergot is taken in toxic amounts, the patient complains of pain in the stomach, nausea, thirst and thoracic oppression. Blood may be seen in the vomitus. Severe abdominal cramps are sometimes present and the urine often contains macroscopic blood. The temperature is subnormal and the extremities are cold. Death takes place ofttimes after convulsions, delirium or coma. There may be disturbances of vision and speech and the patient may complain of a severe headache and tinnitus aurium. Other nervous manifestations may consist of itching, tingling, hyperesthesia and anesthesia of the skin. In chronic ergotism where this drug has been taken for some weeks, gangrene of the extremities and nutritive and nervous symptoms manifest themselves as a result of arterial spasm. Attention should be called to the fact that, when excessive doses of ergot are taken to empty the uterus, whether with criminal or therapeutic intent, the life of the child is endangered because a prolonged spasm of the musculature of the uterus temporarily stops the respiration of the fetus. It is a serious matter indeed when two lives are placed in danger as a result of the abuse of an ofttimes useful therapeutic agent.

Treatment.—The early emptying of the stomach is of prime importance. For this purpose lavage with large amounts of warm water is useful. Amyl nitrite inhalation, hot baths and alcohol have been advised to relieve the peripheral vascular spasm. The patient should be surrounded with blankets and external dry heat applied. Castor oil should be administered to cleanse the lower intestinal tract. The exhibition of strychnin and camphor is often necessary to restore circulatory function. Hot coffee enemata have been advised.

CAUSTIC AND GENERAL PROTOPLASMIC POISONS

General.—The members of this group are all active local or general poisons. They are usually employed per orem, although in no small number of cases these agents are introduced into the vagina with the intent of more directly reaching the pregnant uterus and producing its evacuation. The acid caustics cause marked destruction of tissue whether brought into contact with gastro-intestinal or vaginal mucous membranes. The metals and inorganic salts frequently produce a general systemic toxicosis in which the fetal contents of the uterus share. The dead fetus acting as a foreign body is then expelled. The danger to the life of the mother from the use of these drugs whether employed per vaginam or per orem is dependent upon the rapidity and completeness of absorption and the amount of mucous membrane exposed to the destructive action of the corrosive poison. In order to produce the emptying of the uterus by agents of this class, there must be a poisoning of the whole body of the unwilling mother and the death of the child is but an uncertain incident and may not occur until that of the mother takes place.

Acids.—It is obviously impossible in the scope of this article to detail again here the symptoms and treatment of acute poisoning resulting from the use of members of this group as abortifacients. These subjects are dealt with at length in a special discussion of caustics in another part of this work. It should be sufficient to state that the motives prompting the taking of any of these poisons, whether for suicidal or feticidal purposes, in no way alter the symptom picture or the treatment indicated. Administration of the corrosives by vagina gives rise to extensive destruction of the mucous membrane of the birth canal with subsequent contraction and stenosis if the life of the mother is preserved. Lewin reports a case in which ½ liter of sulphuric acid was injected per vaginam although the uterus was not emptied as a result of this procedure, a dead child being delivered through an abdominal incision. If the poison fails to produce abortion and the child goes to term, subsequent delivery is fraught with considerable difficulty and a mutilating operation with death of the child is often necessary.

To determine the exact corrosive used may offer some difficulties, but the charring of the mucous membrane with sulphuric acid and the yellow stain of nitric acid resulting from the local use of these acids are quite distinctive. The odor of acetic acid and the white stain of phenol aid in determining the drug used.

Metals and Inorganic Salts.—Of this group mercuric chlorid, phosphorus and alum are most frequently employed both by mouth and in the vagina. Bichlorid of mercury douches are not rarely used as a contraceptive and probably for this reason the woman who does not desire her pregnancy to take the normal course ofttimes concludes that the use of corrosive sublimate will act as an abortifacient. Dr. J. C. Hirst informs me that the insertion of bichlorid tablets into the vagina with the intent of producing an abortion is not an infrequent occurrence. Bland reports 3 cases with 2 deaths in which from 15 to 60 gr. (1 to 4 gm.) of mercuric chlorid were introduced into the vagina. The symptoms vary in no way from those caused when this drug is taken by mouth save for the violent reaction of the vaginal mucous membrane. McPeek has reported a case in which 7.5 gr. (0.5 gm.) of this drug were placed in the vaginal canal as a contraceptive, symptoms appearing in two hours, urinary suppression in seventy-two hours followed by a tedious recovery covering a period of four months. Rarely after a bichlorid douche a very violent and rapidly fatal peritonitis ensues and this result is believed by Sexton, who reports such a case, to be due to the fact that some of the poison is injected directly into the peritoneal cavity through the uterus and patulous fallopian tubes. An autopsy on the case above referred to seemed to prove this theory. The general symptom picture of bichlorid poisoning following vaginal absorption varies but little from that cited elsewhere in this text. There is always a violent early vaginal and pelvic reaction with burning vulvar pain, bloody or mucopurulent vaginal discharge and marked congestion and swelling of the labia. Salivation, nausea, vomiting, diarrhea and urinary suppression are symptoms which are manifested promptly.

Arsenic is usually taken by mouth but occasionally is introduced into the vagina. In the latter case pronounced local vaginal distress is experienced with extensive necrosis and sloughing. Vesicovaginal or rectovaginal fistulæ may follow this tissue destruction.

In England pills made from diachylon (lead oleate) seem to be a popular agent for the production of abortion. Aloes, bitter apple, or some of the other reputed abortifacients are usually added to this preparation. The symptoms are those of acute or chronic lead poisoning dependent on the amount of the drug contained and the period of time over which it is administered.

When potassium chlorate is ingested the result is usually very fatal for both the mother and the child. The death of a girl who took potassium chromate to produce abortion is mentioned in the medical literature. Potassium permanganate is rarely used and is often neither effectual nor rapidly harmful in its action. Iron and alum have been used but are neither efficient nor harmful.

Gases.—The gaseous substances are but rarely employed. Carbon monoxid is sometimes inhaled but not infrequently, due to the despondent state of mind of the pregnant woman, the motive is suicide rather than a desire to produce an abortion. Whatever the motive, death results with great regularity when this gas is inhaled in any considerable quantity.

Carbonic acid is very rarely used either by mouth or vagina as an abortifacient, but it may be stated as a general rule that any overloading of the blood-stream with this gas would be harmful to the child in utero.

Organic Substances.—The members of this group are not frequently deliberately used to empty the uterus. An excess of alcohol in the maternal blood produces a deleterious effect on the fetus whose blood is subjected to a like concentration of the substance. The symptoms of alcohol poisoning are too well known to justify enumeration here. The rarity of the use of nitrobenzol and anilin demands only mention of their ingestion as possible with the intention of producing abortion. While not acting physiologically, as do many of the members of this class, the alkaloids, strychnin, nicotin, pilocarpin and atropin should be mentioned as drugs which have been used with the intention of producing abortion. Strychnin in toxic doses exerts its excitomotor effects and the classical convulsive picture makes the cause not difficult to determine. Atropin acts as a delirifacient and nicotin as a cardiac and nerve poison. When poisoning by nicotin takes place, an infusion of tobacco has usually been injected into the vagina or lower uterine segment. The symptoms are often very prompt. For further elaboration on the toxic symptoms observed in nicotin poisoning the reader is referred to the more complete discussion of this subject elsewhere in this work. Pilocarpin in toxic doses produces a great increase in the lacrimal, salivary and sweat secretions, nausea, vomiting and profuse diarrhea. There is pupillary contraction and cardiac palpitation and arhythmia. Death may occur from paralysis of the heart or edema of the lungs.

Treatment.—When any of the caustic acids have been injected into the vagina, the first indication is to limit in so far as possible the corrosive action. Copious vaginal douching with 5 per cent sodium bicarbonate solution or with warm water is indicated. Mucilaginous or demulcent solutions are very useful to allay the violent irritation and inflammation. The prevention of secondary contractures or stenoses is almost impossible and the physician must depend on plastic operations later to relieve the resulting vaginal deformity. Cleansing the birth canal frequently with a bland alkaline solution will lessen the absorption of necrotic substances. When the acids are taken by mouth the treatment is that outlined elsewhere in this text.

In poisonings by metallic substances or inorganic salts, combined vaginal and systemic treatment should be administered when they have been used per vaginam. The removal of the offending substance from the birth canal and the very prompt administration of antidotal remedies by mouth to combat that portion of the drug which has been absorbed are the chief indications. When mercuric chlorid has caused the poisoning, calcium sulphid by mouth and vein or, if not procurable, Carter's antidote employed in the same manner should be administered in connection with alkaline diuretic treatment. In arsenical poisoning the administration of the official antidote and the painstaking cleansing of the whole intestinal tract are steps of prime importance. The physician must not neglect to remove from the stomach by lavage that portion of the drug which is thus excreted. If this drug is taken by mouth, of course the cleansing of the vaginal canal is not required. The treatment for the shock, diarrhea and dehydration observed in this poisoning need not be again elaborated at this time.

When diachylon pills or other preparations of lead have been used, the treatment consists of morphin for the colic, salines, cardiac and respiratory stimulants and external heat for the collapse.

The limitations of this article forbid more extensive elaboration of the symptoms and treatment for poisoning by the less frequently used drugs of this group. It should be sufficient to add that the prompt removal of those drugs from the gastro-intestinal or vaginal canals when no specific antidotal remedies exist and the meeting of general symptomatic indications is usually sufficient. When carbon monoxid has been inhaled for abortifacient purposes, treatment to be successful must be very prompt. As discussed earlier in this text, removal of the patient to the fresh air, the exhibition of oxygen and the employment of artificial respiration are the chief means of combating the asphyxia. The treatment of alcoholic poisoning is too well known to justify repetition. When chloroform has been inhaled in excess, artificial respiration, cardiac stimulants, external heat, and other cutaneous stimuli are to be employed. In poisoning with nitrobenzol, removal of the poison from the gastro-intestinal or vaginal tracts, stimulation of the cardiac apparatus and the avoidance of the administration of fats are indicated. Anilin poisoning calls for gastric lavage, stimulation and general supportive measures, such as external heat and hot coffee enemata. Artificial respiration is often necessary. Transfusion of blood has been suggested.

Diagnosis of Abortifacient Poisoning.—Not infrequently the physician has brought to his attention a patient suffering from indefinite symptoms to which he can assign no reasonable cause. The presence of an abortifacient drug toxicosis may not suggest itself to him until he concludes taking his history and has in his possession facts relative to menstrual regularity, social state, number of children in the family, age of the youngest child, the wages of the husband, etc. In not a few cases an indefinite group of gastro-intestinal or genito-urinary symptoms coupled with the knowledge that the patient does not welcome the present pregnancy points to a possible explanation of the illness. If the patient is widowed or divorced or if the wages of the husband are insufficient to support the present family or if there is a desire for a social or financial prominence which might be interfered with by the addition of another child to the family responsibilities, these facts might offer a clue to the true state of affairs and lead to the correct diagnosis. Rarely does the conscience of the patient prompt her to confide in the physician the nature of her trouble. Fear of death sometimes so quickens a leaden conscience that the use of an abortifacient is confessed. A vaginal examination should not be omitted as a routine procedure and if this rule were more frequently carried out there would be less delay in making what ofttimes is not a difficult diagnosis. When specific symptoms are present such as a lead line on the gums, the practitioner knows to a certainty that a particular drug has been absorbed and the vaginal canal should not be overlooked as a possible avenue of entrance for the poison. A careful study of the urine and feces for evidences of chemical poison must not be neglected. Finally, whenever the patient is a woman and if the symptoms can reasonably be ascribed to the effects of any of the reputed abortifacients, position in society, church or home must not blind the diagnostic vision of the physician to the possibility of an attempt to relieve a pregnant uterus of an unwelcome occupant.

General Comment.—It is not possible to gage the dose of any of the drugs mentioned above so that abortion will result and at the same time the life of the mother will not be put in jeopardy. Lewin states that the difference between the abortive dose and the lethal dose for the mother becomes less with the increasing age of the fetus. The greater amount of poison to which it is subjected in proportion to its size and the relatively loose attachment of the young ovum to the uterine mucous membrane are also ascribed by Lewin as factors explaining the more marked efficiency of drug abortifacients in early pregnancy. These facts relate to the present discussion only in so far as the patient in advanced pregnancy is led to take increasingly larger doses when the poison is not successful in smaller quantities. Finally, the best but most difficult treatment is preventive in character. If the moral standards of all the members of the medical profession were so lofty that none stooped to feticide and if the immoral midwife could be made moral and the public conscience awakened to condemn this practice universally, much misery and suffering would be avoided.

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CHAPTER XL

POISONING FROM MEDICINAL DRUGS

Frank P. Underhill

ARSENIC

The characteristic features of arsenic poisoning are elicited by arsenious acid ($As_2O_3H_3$) and its salts or by the anhydrid (As_2O_3) which is often spoken of as arsenic. The influence of arsenic is due to the ion of arsenious acid and not to the element. This conception readily explains the fact that compounds of arsenic, such as arsenic acid (H_3AsO_4) and its salts, and organic compounds of arsenic, both of which dissociate less readily, are much less toxic than arsenious acid. Upon entrance into the body these latter substances only gradually dissociate, forming arsenious acid in the tissues from which typical arsenic poisoning may occur. It is therefore quite evident that poisoning by arsenic is characteristic even though the source of arsenical compounds may be quite varied and the number of arsenical preparations larger.

The forms of arsenic most commonly prescribed follow: arsenious oxid (As_2O_3); Fowler's solution (contains 1 per cent solution of arsenious anhydrid rendered alkaline with potassium bicarbonate, to which compound tincture of lavender is added to give flavor and color); sodium arsenate ($Na_2HAsO_4 + 7H_2O$); anhydrous sodium arsenate ($NaHAsO_4$); Pearson's solution (1 per cent solution of dried sodium arsenate; arsenious iodid (AsI_3); Donovan's solution (contains 1 per cent of arsenic iodid and 1 per cent of red mercuric iodid); cacodylates; atoxyl or sodium arsanilate ($NH_2C_6H_4OAsOH.ONa$); arsacetin (acetyl atoxyl); arsphenamin (p. dihydroxy-m-diamino-arsenobenzene) ($HCl\ NH_2OHC_6H_3As$); neo-arsphenamin (Sod. diamino-dihydroxy-arseno-benzene-methanal sulphonylate) ($AsC_6H_3OH\ NHCH_2O\ SO\ Na$); silver arsphenamin.

Irrespective of the method of administration, arsenic exerts a poisonous action calling forth characteristic symptoms and inducing pathological changes.

There are at least three distinct types of arsenic poisoning, namely, an acute, a nervous and a chronic form.

Acute Arsenic Poisoning.—The acute form of arsenic poisoning includes all those cases in which the inflammatory symptoms are severe from the beginning and in which the patient dies within twenty-four hours or may survive for two or three days. Usually symptoms appear promptly but may be delayed for from one-half to one hour. This is especially true when large doses have been taken. The first symptoms appear to be dryness and constriction of the throat, with difficulty in swallowing and general discomfort in the stomach. Violent pain with nausea and vomiting follow. The vomited matters at first consist of food substances together with part of the arsenic swallowed. Later the vomitus may contain bile or blood or consist of a clear fluid. Diarrhea soon sets in with colicky pains. The fecal matter passed at first has the general characteristics of diarrheal stools; later, however, it may partake of the nature of the rice-water stools of cholera. As such it consists almost entirely of small particles or shreds of disintegrated mucous membrane suspended in a somewhat serous fluid. At times, however, the stools are clear. From the great extraction of water from the body by way of the gastro-intestinal tract, there is thirst and the urine may be greatly diminished. Indeed, a condition of anuresis may develop in large measure owing to the action of arsenic upon the kidney. If urine is excreted it may be albuminous or even bloody. Accompanying these gastro-intestinal manifestations, nervous symptoms may intervene, consisting of dizziness, headache and pain or cramps in the muscles, chiefly of the limbs. The skin is cold and damp and the extremities are cold; cyanosis may be present; there is a feeble pulse with weak, sighing respiration. Toward the end there is collapse which may pass into coma or there may be convulsions or general paralysis with death. Death is perhaps due in large part to exhaustion. In some instances death does not follow immediately, the patient recovering from the acute effects only to develop chronic arsenic poisoning. The fatal dose is uncertain, death having occurred from quantities as small as 0.1 gm. (1½ gr.).

Nervous Arsenic Poisoning.—In the nervous type of arsenic poisoning the usual symptoms associated with gastro-intestinal disturbances may be slight or even entirely absent. This type is characterized by the influence upon the nervous system. The chief symptoms that may be manifested are narcotism, paresis, deepening into paralysis, delirium, and even acute mania and convulsions. These cases are not common but occasionally one occurs and attention is called to the possibility since the symptoms encountered are so unlike those usually seen in arsenic poisoning.

Chronic Arsenic Poisoning.—Chronic arsenic poisoning may be initiated either by the ingestion of a single large dose or the repeated administration of small doses. The latter is the more common method of its induction. In the therapeutic use of arsenical preparations the earliest form of intoxication is manifested by diarrhea, colicky pains, conjunctivitis or swelling of the eyelids. There may be sensations of weakness, loss of appetite, nausea, occasionally vomiting, and even constipation may result. Should the arsenic be continued, the second phase of chronic arsenic poisoning soon sets in. This is characterized by inflammation of the conjunctiva, coryza, sneezing, hoarseness and cough arising from an inflammatory reaction upon the mucous membranes of the nose and larynx. Jaundice may appear with swelling of the liver. Skin eruptions are usually quite marked, the so-called "eczema arsenicale." These may take the form of exfoliation, the skin falling off in fine brownish flakes, or even in large flakes, especially on the hands and feet. The hair falls out and the finger nails may become loose or detached. Again an acnelike eruption may appear. A form of melanosis is also quite prominent, which is probably caused by the formation in the layers of the skin of organic pigment granules. It has been erroneously assumed that the pigmentation is caused by deposition of arsenic in the skin. This symptom is much more prominent in individuals of dark complexion than in those with a fair skin. In the latter it partakes more of the nature of freckles. Usually this arsenic melanosis, so-called, disappears when the individual becomes arsenic-free, but in some instances the pigmentation is permanent. Chronic intestinal catarrh develops which ultimately may lead to ulceration. When the poisoning is very slow there is persistent capillary paralysis leading to widespread fatty and other degeneration. The endothelium of the capillaries is first attacked, subsequently the cells of other organs and tissues, particularly the liver, kidney and heart muscle. There is also considerable tendency for the development of local effusions.

The symptoms referable to the third phase of chronic arsenic poisoning are indicative of an action on the peripheral nerves giving rise to polyneuritis, atrophy of the muscles involved, disturbance and paralysis of sensation which may involve the eye producing blindness. This phase of poisoning is initiated usually by intense headache, or acute pain in the knee, ankle or foot. It is less commonly observed in the hand or wrist. The palms of the hands and the soles of the feet become red and swollen and are extremely sensitive to pressure.[1] The sensory paralysis, especially of the extremities, closely resembles that of locomotor ataxia. In the later development of motor paralysis, which is usually confined to the extremities, and generally although not invariably symmetrical, diagnosis of arsenic poisoning is sometimes quite difficult, the disturbances closely resembling those seen in lead poisoning and in alcoholic neuritis. If other differentiation fails, the urine and hair should be tested for arsenic. If the period of poisoning is prolonged, the individual sinks into an apathetic, semi-idiotic condition, or indeed may become epileptic. If the poison is removed, the condition generally improves and the symptoms disappear although some trace of paralysis may persist for years. If the muscles are markedly degenerated, little hope of improvement may be anticipated. Death is usually by malnutrition and exhaustion, emaciation being a striking feature.

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[1] Keratosis of the palms and soles may follow.—Editor.

Pathology of Arsenic Poisoning.—The most marked changes to be observed are the fatty degeneration and infiltration of the liver and kidney. This change in the liver may proceed to such an extent that the entire organ is distinctly yellow. In acute poisoning there may or may not be evidences of an inflammatory reaction either in the stomach or intestines or in both. The inflammatory changes may be recognized many months after death since the presence of arsenic in tissues tends to prevent or at least to retard putrefactive changes.

Treatment of Arsenic Poisoning.—Acute arsenic poisoning is best treated by lavage with warm water. The lavage should be continued until one may be assured that all the arsenic has been removed from the stomach. If lavage is impossible, emetics should be employed. They are not so effective, however, as lavage and are detrimental inasmuch as they tend to induce depression. Whichever treatment is carried out should be prompt. Attempts to wash the intestine by high rectal tube are usually of little value. When the stomach has been thoroughly washed the intestine is best emptied by purgatives. For this purpose the saline cathartics are to be preferred since they act promptly. Chemical antidotes, such as the so-called "arsenic antidote," are of doubtful value. It is much better to rely on repeated and copious lavage with subsequent purgation. The collapse usually observed in acute arsenic poisoning is to be treated by the ordinary measures employed, such as warmth and stimulants, for example, caffein and digitalis. In view of the water deprivation of the body incident to the extensive vomiting and diarrhea, large volumes of fluid should be administered over a period of three or four days. Such a procedure will also facilitate the excretion of that portion of the arsenic absorbed.

In the treatment of chronic poisoning the cause should be removed and symptomatic measures taken. The paralysis may be combated by stimulating the muscles with the galvanic current.

Toxicology of the Arsphenamine Group.—In the use of arsphenamin and neo-arsphenamin there are a certain number of cases that exhibit systemic effects which are not completely understood. The percentage of cases in which the reactions occur varies from 1 to 15 per cent. In most instances the symptoms are alarming and distinctly annoying to the patient, but only occasionally is there a fatality. There are several types of reaction elicited by these compounds.

Type A—Nitritoid Reactions.—In the first type, which is spoken of as the "nitritoid" reactions, there may be vasodilatation, as in nitrite action, hence the name which characterizes this group. If the reaction is very severe the symptoms partake of the nature of anaphylaxis. The symptoms may start during the intravenous injection or immediately after. There is flushing of the face, inflammation of the conjunctiva, an anxious expression, peculiar burning sensation of the tongue, nausea, vomiting and profuse perspiration, edema of the tongue and eyelids. Sometimes there is cough and dyspnea, precordial distress and cyanosis. The pulse is full at first, then weak with a pallid skin. Unconsciousness with feeble pulse may intervene in the severe cases. At times during the period of injection there may be severe lumbar pain. The symptoms thus indicated may disappear within from fifteen to thirty minutes or may grade into the group of symptoms described below as Type B. The symptoms observed immediately usually give place to speedy recovery even though there is a condition of actual collapse. The condition of actual collapse is much more frequent following the second dose.

The cause for the nitritoid reactions has been variously given. It has been ascribed to lack of purity in the preparations employed, the impurity being spoken of as substance "X"; to a "colloidal reaction," precipitation or "anaphylaxis"; to the liberation of decomposition products, which, however, are usually less toxic than the original substances; to the formation of an insoluble base, by certain salts of the blood, which forms emboli; to a special supersensitiveness to the drugs themselves. Of the foregoing hypotheses the most likely appear to be associated with the presence of substance X and the susceptibility of the patient.

Treatment of Nitritoid Reactions.—In the treatment of nitritoid reactions, epinephrin may be employed prophylactically and after appearance of symptoms. If used as a prophylactic, 1 mgm. may be administered intramuscularly just before the injection of the arsphenamin compound. If symptoms have arisen, ½ to 1 mgm. may be given intravenously. Good results have been reported by this treatment. If the individual is susceptible to arsphenamin, it is quite possible that he will also exhibit sensitiveness to epinephrin resulting in symptoms quite as alarming as those induced by the arsphenamin compounds.

Type B—Early Symptoms.—These symptoms consist of chilliness or a distinct rigor, headache, vertigo, nausea, vomiting, diarrhea, and rise of temperature, usually from 100° to 102° F. All of these symptoms may not be present and the patient may merely feel "queer" or there may be chills, attacks of emesis and profuse and protracted diarrhea. Sometimes complaints are made of severe pains in the legs and back. This group of symptoms usually passes off in from twelve to fourteen hours and is followed by a feeling of lassitude and weakness. More rarely vomiting and diarrhea with slight rise of temperature may continue for a number of days, nourishment not being retained during this period. Sometimes the urine is small in volume and may contain albumin and casts. Various types of eruptions may appear within a few hours or not for several days. The most common are urticarial, scarlatinoid, morbilliform erythemas, rarely purpura. Sometimes an itching of the skin or pruritus without accompanying eruption may be observed. Generally these eruptions disappear within a day or two. Late eruptions occurring from six to ten days after the administration of the drug are much more persistent, universal exfoliating dermatitis occurring which may last for weeks with fever and debility and at times ends in death.

Type C—The Late Symptoms.—The reactions may be delayed for more than twenty-four hours, in which event they usually consist of vomiting, fever and diarrhea, similar to the immediate reactions. More rarely serious and even fatal reactions may develop about three days after the administration of the drug. In these instances the symptoms are referable either to the brain or to the liver. In the severe cases there may be headache, vomiting, muscular twitchings, epileptiform convulsions, dilatation of the pupils, absent reflexes, coma and death. These symptoms are usually the expression of edema of the brain or of encephalitis hemorrhagica. A rare syndrome subsequent to arsphenamin administration is characterized by severe jaundice accompanied by rise of temperature. This may appear in from three days to several weeks after treatment. Most cases pursue a favorable course but sometimes a fatality occurs with the symptoms and autopsy findings of acute yellow atrophy of the liver.

The *treatment* of the later manifestations of poisoning by the arsphenamin group is purely symptomatic.

MERCURY

Salts of mercury may be regarded as protoplasmic poisons. In virtue of this property, mercury salts are active germicidal agents. Their relative insolubility, ease of precipitation, distinctly irritative and toxic properties necessarily limit their wide application. In general, as with arsenic, poisoning occurs only when the salts are dissociated. In this instance, however, the poisonous action is associated with the mercury ion, which is very reactive chemically, combining with protein and usually forming an insoluble compound. The mercurous salts in general are less irritative and less toxic than the mercuric salts because of greater insolubility. Certain of the organic mercury compounds, such as "mercurochrome 220" of Young, and mercurophen, are not irritant although retaining antiseptic properties. The relatively low toxicity and non-precipitation of protein by these compounds are consequences of the non-ionized condition of the substance. Whatever type of mercury compound is employed, it may, under favorable conditions, give rise to typical mercury intoxication.

Some of the more common mercury compounds that may cause poisoning when employed medicinally are the various preparations containing metallic mercury, such as Blue Mass or Blue Pill containing 33 per cent of mercury, and used like calomel; unguentum hydrargyri for inunction —50 per cent mercury in suet or lard; or the more dilute Blue Ointment (30 per cent mercury) for cutaneous parasites; calomel; calomel ointment; yellow mercurous iodid; black mercurial lotion (black wash); ammoniated mercury in various compound ointment bases; yellow mercuric oxid and red mercuric oxid in various ointments; corrosive sublimate; potassium mercuric iodid; mercury salicylate; citrine ointment; organic mercury compounds such as mercurophen, mercurochrome 220, and chloromercurphlorescin.

Mercury compounds are readily absorbed from mucous membranes and even from the skin. Mercury disappears rapidly from the blood and is deposited in the various organs probably as compounds of proteins of the cells. Excretion occurs both through the feces and urine and even after a single dose may continue for several days. When mercury has been given continuously for a considerable period its excretion may be a matter of months. Mercury poisoning may be classed into three types—acute, subacute and chronic.

Acute Poisoning.—The earliest symptom of excessive therapeutic use of mercury is stomatitis. First the breath has a fetid odor, there is a metallic taste, the gums are sore (gingivitis) and salivation (ptyalism) occurs. This stomatitis occurs about as readily when mercury is given otherwise than per os. If the therapeutic administration is continued the edges of the gums become black and the teeth loosen. Later the gums and tongue are swollen and ulceration may occur. Infection sets in and combined with the accompanying irritation very severe salivation and progressive exhaustion develop. In the advanced stages the teeth may be lost and necrosis of the jaw may occur. Some grade of stomatitis may even follow the single administration of calomel in certain individuals.

In the more acute types of poisoning the immediate effects are corrosion and irritation. There is a metallic taste, salivation is pronounced, the mouth and pharynx are ashy in appearance with a burning sensation, swelling of the mucous membrane may occur, and sometimes edema of the glottis is present. There is thirst with abdominal pain, colic, and vomiting with white or bloody mucous shreds. These symptoms usually yield to local treatment, including fasting for one or two days, and the patient seems quite well. Symptoms of stomatitis may appear during the first twenty-four hours.

After absorption the poison appears to act chiefly upon the large intestine and upon the kidney. Generally within from two to three days the urine contains albumin and is greatly diminished in volume; indeed, anuresis may develop followed by death without convulsions in about one week. If the kidneys have not been too severely injured a membranous colitis sets in, accompanied by dysentery, tenesmus, ulcerations, hemorrhages and degeneration of the liver. Death may not occur for weeks. In the most severe cases blood-pressure may fall from cardiac involvement and there may be vasomotor disturbances, feeble pulse, insensibility of the skin, coma and collapse. Consciousness is usually maintained unimpaired. Sometimes giddiness is experienced or the patient is sleepy and again anxiety and restlessness may be observed.

Should recovery from the acute stage occur, subacute poisoning may set in which is characterized by nephritis, stomatitis, and colitis. Sometimes skin eruptions are present. This syndrome is frequently seen in poisoning from the medicinal use of mercury. Usually the stomach and small intestines are not involved.

When mercury poisoning occurs from use other than by mouth the local symptoms are absent.

The kidney appears to be affected even after the ordinary medicinal use of mercury, for some albuminuria is frequently present owing perhaps to damage to the renal tissue in its effort to eliminate the poison. When the injury is slight the nephritis partakes of the nature of the interstitial form, although the glomeruli and also the epithelium may be affected. Later cirrhosis may develop. If the nephritis is acute it involves the tubules primarily, although with severe injury hemorrhagic glomerular nephritis may be induced. Sometimes various portions of the kidney may contain crystals of calcium carbonate. The formation of these crystals is not understood.

The cause for stomatitis, colitis and nephritis is usually attributed to injury of membranes involved during the process of elimination.

Postmortem Findings.—If the poison has been taken by mouth the mucous membranes of the alimentary canal may be ashy colored, congested or corroded. The colon especially may be the seat of inflammation. The kidneys show acute inflammation with calcification. When mercury has been parenterally administered, the colon and kidneys show the most change.

Treatment of Stomatitis.—During the administration of mercury the mouth and teeth should be in the best condition possible. Both from the viewpoint of prophylaxis and of treatment, a mouth wash, hydrogen peroxid or potassium chlorate (a tablespoonful of the saturated solution to a glass of water), should be used several times daily. The addition of a little tincture of myrrh will improve the taste of the mouth wash.

Treatment of Acute Mercury Poisoning.—If the poison has been taken by mouth, promptness in treatment is of prime significance and consists in precipitation in the stomach of the mercury as a non-corrosive albuminate. For this purpose white of egg or milk may be given. The mercury-protein compound thus formed should be promptly removed from the stomach by lavage preferably or by use of an emetic. If the poison has had time for absorption, this treatment will be less effective. On the other hand frequent lavage of the stomach is of distinct value. Equally efficient but less convenient as an antidote is a hypophosphite-peroxid mixture (sodium hypophosphite 1 gm., water 10 c.c., and hydrogen peroxid 5 c.c., estimated for each 0.1 gm. of mercuric chlorid). Lavage with the diluted solution should follow this treatment. In order to protect the kidneys as much as possible, a light diet should be given with a plentiful supply of fluid so long as the kidney remains sufficiently active. The administration of sodium bicarbonate may also aid in protecting the kidney from damage.

A detailed outline of treatment which embraces the above principles is that of Lambert and Patterson as follows:

"The first indication is to give the patient the whites of several eggs and then to wash out the stomach thoroughly. This has usually been done before the patients are admitted to the hospital. On admission, the stomach contents are expressed and examined for mercury, the stomach is thoroughly washed, and a pint of milk introduced. If no stomach contents are obtained before lavage, then the lavage water is examined for mercury. The metal appears in the urine in from three to twenty-four hours after it has been swallowed. If more than a day has elapsed since the poisoning occurred, a stool should also be examined for the poison. If the first lavage does not allay the nausea and vomiting, it is repeated after an hour, and the following routine is begun as soon as the stomach will permit:

"1. The patient is given every other hour 8 ounces of the following mixture: potassium bitartrate, 1 dram; sugar, 1 dram; lactose, ½ ounce; lemon juice, 1 ounce; boiled water, 16 ounces. Eight ounces of milk are administered every alternate hour.

"2. The drop method of rectal irrigation with a solution of potassium acetate, a dram to the pint, is given continuously. The amounts of urine secreted under the treatment are very large.

"3. The stomach is washed out twice daily.

"4. The colon is irrigated twice daily, in order to wash out whatever poison has been eliminated in that way.

"5. The patient is given a daily sweat in a hot pack.

It is imperative to emphasize the necessity of keeping up the treatment with the colonic drip enteroclysis day and night without interruption."

When poisoning is not severe a week may be a sufficient time for treatment. When large or successive doses have been taken, or when there is a preëxisting kidney lesion, or when treatment begins several days after the poison has been taken, longer periods, even up to three weeks, are necessary. When cases have reached the stage of anuresis favorable results cannot always be expected.

A variety of treatments have been proposed aimed to render less active mercury that has been absorbed. None of these has proved of distinct advantage.

Chronic Mercury Poisoning.—In chronic mercury poisoning there is at first loss of appetite, nausea and gastro-intestinal symptoms with constipation or diarrhea followed by loss of weight, anemia, and pains in the bones and joints. A general cachexia may result. Unlike lead poisoning there is no line on the gums, but there may be a gingivitis. Nervous symptoms may be pronounced. The most prominent are tremors, usually of the hands and lips, although the whole body may be affected. Psychic irritability, restlessness, mental weakness, loss of will power, various psychoses, and rarely a peripheral neuritis, muscular atrophy, decalcification of the bone, are symptoms that may be encountered.

Treatment of Chronic Mercury Poisoning.—There is considerable doubt whether treatment materially modifies the patient's condition. Everything possible should be done to promote elimination of the poison, such as administration of water and perhaps alkali. Potassium iodid is generally recommended but the efficacy of the treatment is very doubtful. For the rest, treatment is purely symptomatic, attention being given to the malnutrition, the anemia and to the nervous manifestations.

SILVER

Silver is employed mainly in the form of the nitrate or as protein compounds because of the antiseptic properties of silver. Caustic silver nitrate is also extensively used locally in various affections for purposes of cauterization. In present-day therapy argyrism, or a bluish-black discoloration of the skin, rarely occurs. In true argyrism the coloring is permanent but no symptoms arise. The application of silver salts to the skin or mucous membranes causes stains which are quite distinct from argyrism. These stains may be removed by 10 per cent potassium iodid or cyanid.

Poisoning from silver usually occurs by the accidental swallowing of pieces of the caustic (lunar caustic) silver nitrate, especially in infants during the treatment of various conditions of the mouth and lips. Swallowing the caustic causes pain in the throat and stomach, vomiting, gastritis and later diarrheal stools which may show blood. If absorption of the silver occurs, dizziness, convulsions, and coma may supervene.

The postmortem appearances show the local action of the caustic. Stains on the mucous membranes of the esophagus and gastro-intestinal tract will be white at first but will turn black on exposure to light. Inflammation in the stomach and intestines is present.

Treatment of Silver Nitrate Poisoning.—Large volumes of common salt and water (dilute solutions) should be given either as lavage or in combination with an emetic. Usually the salt water itself will act as an emetic. The salt forms the insoluble silver chlorid which is not as irritating as the caustic silver nitrate. Lavage should be continued until the wash water no longer gives a test for silver. When this point is reached, eggs and milk may be prescribed for their demulcent effect.

BISMUTH

Under ordinary circumstances even very large doses of bismuth given by mouth are harmless. Under special conditions, however, bismuth salts may become poisonous. The insoluble bismuth salts are employed in X-ray diagnosis, and as adhesive powders forming a protective membrane on inflamed mucous surfaces and on wounds. The subnitrate and subcarbonate are useful against diarrhea, gastritis and gastric ulcers. Bismuth paste applied to chronic suppurative abscesses and sinus may give rise to toxic symptoms. A certain amount of the basic bismuth salts may be dissolved by the gastric juice, absorbed into the circulation and find elimination through the intestine, kidney and mouth. Usually the amount thus absorbed is too small to produce symptoms. In cases of poisoning, bismuth may be found in the kidney, stomach, and liver. Formerly some samples of bismuth subnitrate contained traces of arsenic, antimony, lead and tellurium, and cases of poisoning from these impurities have been reported, arsenic being the chief offender. With more perfect methods of preparation, contamination with these substances is no longer probable.

Bismuth Poisoning.—This may manifest itself in several ways; (*a*) *nitrite effects* from reduction in the large intestine by bacteria of nitrate to nitrite, the toxic effects therefore being due to nitrite and not to bismuth itself (the symptoms are methemoglobin in the blood, cyanosis, diarrhea, dyspnea and death from respiratory failure). (*b*) *Capillary thrombosis* is formed from the precipitation of hydrogen sulphid in the intestinal vessels. Bismuth sulphid is black and very insoluble. When bismuth is absorbed into the blood, precipitation of bismuth sulphid may take place in the capillaries of the large intestine causing capillary embolism. Later ulceration occurs and vomiting, cramps, diarrhea, colic and colitis may follow. The colitis produced is usually much less severe than that observed with mercury poisoning. A "lead line" may appear upon the gums due to the deposition of bismuth sulphid. At times this spreads in patches on the mucous membrane of the mouth and indeed the entire mouth and tongue may become discolored; stomatitis and loosened teeth may also be in evidence. (*c*) *Chronic bismuth poisoning* in which the symptoms observed are headache, fever, stomatitis, "lead line" and discoloration of mouth and tongue, gastro-intestinal disturbances, diarrhea with black stools, colic, and albuminuria. Unlike lead, bismuth poisoning usually fails to show specific effects upon the nervous system and upon the blood. In some fatal cases convulsions and tetanus may occur.

Treatment of Bismuth Poisoning.—For the nitrite effects emetics or lavage of the stomach may be employed. To counteract the systemic influence, epinephrin or strophanthin may be used. In treatment of specific bismuth poisoning the administration or application of the drug should be stopped and everything possible done to favor elimination of the poison, for example, lavage of stomach, catharsis and administration of large volumes of H_2O. For treatment of the stomatitis see under Mercury.

IODIDS

The employment of iodids, usually in the form of sodium or potassium iodid, may produce local irritation in the stomach and evidences of irritative reactions on the skin and mucous membranes. These reactions partake of the nature of rashes, or of coryza, headache, bronchitis, laryngitis, conjunctivitis. Stomatitis, parotitis and anorexia may occur, but much less commonly. In addition to the general irritation of the mucous membranes of the mouth, throat and trachea, there may be salivation with general malaise. The symptoms referred to above lead the patient to believe he has influenza. At times the laryngitis may be so severe that edema of the glottis occurs. The skin lesions consist of irregularly scattered papules, the chief sites being the face, shoulders, neck and back. In addition to this acnelike appearance, "iodism" may manifest itself in the form of furuncles, erythema, purpura, urticaria and vesication, all of which may be accompanied by fever. The more serious eruptions usually occur in patients with a lowered vitality and are especially prominent in chronic nephritis, perhaps owing to inability to excrete iodids which in the normal individual are promptly eliminated.

Usually the less severe skin eruptions are produced by smaller doses and they sometimes disappear when larger doses are given.

Chronic iodism is characterized by anuria, emaciation, nervous irritability, tachycardia, and loss of sexual power. In general, even though definite symptoms are not in evidence, large quantities or long-continued use of iodids tends to lessen body tone and to depress the spirits.

Susceptibility to iodid action varies greatly. In some patients the symptoms appear in a few hours even after a small dose; in others they are manifest only after long-continued use. The reactions characteristically induced are not confined to iodids but may be caused by any iodin compound. Thus iodoform may produce the symptoms of iodism. It is probable, however, that these reactions occur only after dissociation of the compound with liberation of the iodid ion. Formerly the skin symptoms were referred to excretion of the drug by the sebaceous glands, the view being that free iodin was liberated by the fatty acids of the sebaceous secretions. This idea, however, is erroneous and similar symptoms may be induced by the sulphocyanids which in dissociation fail to liberate an irritative ion.

Treatment of Iodism.—The drug should be discontinued. Great cleanliness, particularly of the mouth, and the administration of alkalis and arsenic are indicated. The catarrhal symptoms may be cleared up in one or two days by the use of calcium lactate in doses of 4 gm. per day, but the calcium treatment should not be prolonged.

BROMIDS

The more commonly employed bromids are those of potassium, sodium and ammonium and, to a less degree, those of lithium, strontium and calcium. So far as one may judge sodium bromid is quite capable of fulfilling all the functions and advantages ascribed to the others since it is to the bromid ion that the remedial effect is due. The bromids are employed chiefly as sedatives to induce sleep or to quiet conditions of hyperexcitability as in hysterical states, Basedow's disease, acute cerebral excitement and meningitis, delirium tremens and convulsions as in epilepsy.

Like the chlorids the bromids are rapidly eliminated through the urine, although there is a tendency for the bromids to accumulate in the tissues. The administration of chlorids tends to hasten the excretion of the bromids.

Bromid rashes frequently occur especially on the face when bromid administration has been continued for a considerable period.[2] These rashes closely resemble those induced by iodids. The reason for the occurrence of these rashes is not clear, a variety of opinions being held but none being without criticism. It is quite probable that the nervous system is involved in some way, since vasomotor disturbances accompany the skin rashes.

Acute poisoning may occur from a single large dose. The symptoms observed are profound depression or apathy, or even a stupor which may last for several days. The respiration is slow and low blood-pressure is in evidence. Bromids alone rarely, if ever, cause death.

Bromism or chronic bromid poisoning results from repeated large doses. There is psychic deterioration, the patient being dull, stupid and apathetic; the face is without expression, pale and usually bears diffuse papules; the memory is weak, speech is disturbed, voluntary movements are sluggish; there may be sexual impotence; somnolence; ataxia, tremors; malnutrition as shown by nausea, gastric irritation, diarrhea or constipation leading to a general cachexia and a lowered resistance.

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[2] Extensive necrotic lesions on the legs are common.—Editor.

Treatment.—Treatment of bromism consists in stopping the administration of the drug and hastening its elimination as much as possible. Pushing the intake of sodium chlorid will aid in this process which should be further assisted by the ingestion of large volumes of water. The nutrition should be improved by careful diet and the depression counteracted by caffein or strychnin.

POTASSIUM CHLORATE

Commonly employed in saturated solution as a mouth wash in cases of sore-throat and stomatitis, especially in mercury poisoning, potassium chlorate frequently gives evidences of toxicity, if swallowed. It should not be taken internally, since as far back as 1879 Jacobi pointed out the serious effects produced when the drug is absorbed. Upon absorption methemoglobin is formed, an indefinite amount of hemoglobin being used up in this way since the chlorate apparently does not enter into the reaction. As a result of this fact the action of chlorate may be very severe, leading to a real asphyxia. Moreover the blood-cells disintegrate, resulting in embolism. Other secondary symptoms which may appear are jaundice, hemoglobinuria, anuresis or suppression of urine, bloody tube casts, delirium, coma and death from nephritis.

The symptoms of poisoning indicate gastric irritation; nausea and vomiting, and diarrhea with pain in the abdomen may occur. Cyanosis, collapse and perhaps terminal convulsions may appear. The nephritic condition has already been mentioned. On autopsy the findings correspond with what might be expected from the symptoms—gastro-enteritis, inflammatory changes in the spleen, liver and kidneys. These organs are enlarged and dark brown in color from the contained methemoglobin.

There is great variation in susceptibility to the drug and herein lies one of the great dangers attendant upon its use. If given in divided doses the toxic effect is greater than if administered in a single dose. The fatal dose varies from 15 to 30 gm., 10 gm. producing toxic symptoms. In one instance death occurred from 11.65 gm. Symptoms begin quickly and death may result in five or six hours, but usually the fatal termination results in six or seven days as a result of the nephritis produced. The chlorate passes through the body unchanged.

Treatment.—Treatment of poisoning with potassium chlorate consists of thorough lavage of the stomach and treatment of the secondary symptoms as they arise.

ACETANILID

Acetanilid forms the basis of many headache powders and the indiscrimate use of these leads often to alarming symptoms and even death in patients with a weak heart. Acetanilid is oxidized to paramidophenol and it is probably to this compound that both the remedial and toxic actions are due. This substance is excreted in the urine in combination with sulphuric or glycuronic acid. The indophenol reaction of the urine is given by this compound.

Acute poisoning usually manifests itself upon the alimentary tract and upon the nervous system. There is burning and swelling of the whole alimentary tract; nausea, vomiting, stomatitis, gastritis, cerebral convulsions and coma. With very large doses there may be sudden profuse perspiration, dizziness, and collapse. Failure of respiration causes death.

In chronic poisoning from acetanilid, cyanosis is characteristic, with a rapid heart and sometimes collapse. There is general weakness, dyspepsia, anemia, and some formation of methemoglobin. There is a tendency toward digestive disturbances, various neuroses, neuralgia, erythemata and eczemata or simple pruritus and at times mild neuritis.[3]

Treatment.—In acute poisoning the common alkaloidal antidotes and lavage should be employed. Symptomatically treatment should be stimulating—warmth, ammonia, brandy, strychnin, atropin. Artificial respiration at times is of great benefit. Epinephrin or strophanthin may be employed to stimulate the heart, if indicated. In chronic poisoning the treatment is entirely symptomatic, except that measures (intake of large volume of fluid) should be taken to hasten elimination.

DIGITALIS

The active principles of digitalis or foxglove are obtained from the leaves of Digitalis purpurea, an ornamental garden flower, which also grows wild both in Europe and America. The active constituents are glucosids and therefore prone to chemical change. The glucosids present in digitalis are divisible into at least four groups: (*a*) Digitoxin, a crystalline alcohol soluble compound of the formula $C_{34}H_{45}O_{11}$, which is probably the most important substance of the leaves. On hydrolysis digitoxin yields a hexose and digitoxigenin. (*b*) Digitalin, an amorphous alcohol-soluble compound of the formula $C_{35}H_{36}O_{14}$ which on hydrolysis yields dextrose, digitaligenin and digitalose. It is about one-half as active as digitoxin. (*c*) Digitalein, an amorphous water-soluble substance which is probably a mixture of closely related compounds. They have typical digitalis effects. (*d*) Digitonin, which is a water-soluble saponin occurring in both a crystalline and an amorphous form. The digitonin has properties similar to saponins, that is, irritant and hemolytic effects and the typical digitalis action is lacking.

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[3] Polycythemia may occur in the early stages and anemia in the later. The liver and spleen may be considerably enlarged.—Editor.

Various other glucosids, notably the strophanthins, have digitalis effects, the action differing quantitatively rather than qualitatively. There is considerable confusion relative to the chemistry of the different commercial preparations. The official strophanthin is strophanthin amorphous, although the same plant, the Kombe, also yields a crystalline strophanthin whose action is very similar. Oubain is a crystallized strophanthin which has about twice the toxicity of strophanthin. It is of particular value for intravenous administration.

Digitalis and strophanthins are of great importance in therapeutics in correcting irregularities of the heart beat as in auricular fibrillation or in chronic dilation of the heart.

Great care in administration must, however, be exercised since digitalis and its allies are highly toxic. The best preparations of digitalis are undoubtedly the tincture and the infusion.

Poisoning from the clinical use of digitalis is not rare, indeed the border line between the necessary efficient therapeutic dose and the toxic dose is so narrow that toxic symptoms may appear simultaneously with the desired therapeutic effects. This toxic action is not permanently harmful, if care in administration and dosage is properly regulated.

Early indications of toxicity are nausea, malaise and headache which may be very severe. Diarrhea sometimes occurs but is more common with strophanthin. The dosage of the drug should either be reduced or stopped altogether when these symptoms make their appearance. In one or two days they usually disappear.

In advanced digitalis poisoning, various heart irregularities may be noted, the most common and the earliest to appear being the result of overstimulation of the vagus, the heart beat dropping to 50 or lower. Extrasystoles are frequent, although the rhythm may be maintained. The next stage of poisoning is partial heart block which may be permanent. Finally there may be muscular irritability of the heart, with extrasystoles and high blood-pressure.

Acute poisoning from digitalis is characterized by the symptoms appearing late and the course of the intoxication being prolonged, death in many instances not occurring for a week or more. The most notable symptoms are nausea, vomiting, diarrhea, slow arhythmic pulse, lassitude, sensory and muscular disturbances. Sudden death with asphyxial convulsions is quite characteristic. The fatal dose of digitalis is quite variable, 2.5 gm. having caused death whereas with 4.0 gm. recovery has been noted. The difference in results appears to be associated with the different degree of absorption taking place, and the effect of vomiting, diarrhea, etc., upon this absorption.

Treatment.—In the simplest type of poisoning treatment consists in stopping the drug and keeping the patient quiet in bed until the symptoms have disappeared. To counteract overstimulation of the vagus atropin sulphate in doses of 1/65 gr. (0.001 gm.) may be given subcutaneously. Atropin action, however, is short-lived, its influence lasting not more than one hour. Bromids, 1 to 2 drams (4 to 8 gm.) of sodium bromid, or morphin sulphate, ¼ gr. (0.015 gm.) and a hot-water bag, or ice-bag over the heart may reduce excessive irritability.

When severe poisoning is present, absolute quiet and freedom from exertion must be maintained, since even the slightest effort may cause circulatory failure and sudden death. The other measures to be followed are purely symptomatic—warmth, stimulants, etc.

In acute poisoning, evacuation of the stomach, catharsis, quiet and general symptomatic treatment are advocated.

EPINEPHRIN

Under ordinary circumstances epinephrin does not cause toxic symptoms. At times, however, especially in excitable or susceptible individuals (particularly patients with Basedow's disease), a few minutes following epinephrin administration there may be excitement, anxiety, tremors, palpitation, precordial distress, rise in pulse and respiration rates, high blood-pressure and a rise in temperature. If too great quantities are given intravenously, death may result from acute dilatation of the heart. In other instances death may be caused by respiratory paralysis. There is also danger of intravenous administration in cerebral arteriosclerosis from rupture of a cerebral artery, owing to the sudden marked increase in blood-pressure. There is some danger that the condition of pulmonary edema may be aggravated when epinephrin is intravenously given in pulmonary edema.

Treatment is purely symptomatic.

NUX VOMICA

Nux vomica is the dried ripe seed of Strychnos nux vomica and contains from 3 to 4 per cent of the alkaloids strychnin and brucin which occur in approximately equal quantities. Both alkaloids have the same type of action in man, although brucin action is only about one-thirtieth to one-eighth as strong as the strychnin effect. Practically, therefore, the action of nux vomica is represented by the strychnin present.

The preparations of nux vomica commonly employed are nux vomica, which officially must contain 2.5 per cent of alkaloids (1 gr. = 0.06 gm.); the extract, 16 per cent of alkaloids (1/6 gr. = 0.01 gm.); the fluid extract, 2.5 per cent (1 minim = 0.06 c.c.); the tincture, 0.25 per cent (10 minims = 0.6 c.c.). The official salts of strychnin are the nitrate and sulphate.

Strychnin increases the reflex excitability of the spinal cord and of the medullary centers. The chief action is on the gray matter of the cord. In larger doses tetanus is produced together with marked changes in blood-pressure and spasmodic respiration. Death results from asphyxia induced either by paralysis of the respiratory center or continued contraction of the respiratory muscles.

The first signs of strychnin poisoning consist of restlessness, nervousness, abrupt movements, and stiffness of the face muscles. These symptoms are soon succeeded by more pronounced twitchings of the muscles which may partake of the nature of muscle spasms and lead to general convulsions of the spinal type. In these convulsions all the voluntary muscles are involved, so that of two opposing sets of muscles the stronger predominates. The extensor muscles usually being the stronger, the legs, arms and back are extended and the head is thrown back, the whole action at times being sufficiently aggravated so that the back is arched, the weight resting upon the heels and back of head (episthotonos). The hands are clenched, eyes open and the lips may part in a characteristic grin, the *risus sardonicus,* from the fact that the corners of the mouth are spasmodically drawn out. The patient's mind is clear, which leads to great anxiety, and during the convulsions there is great pain from the muscle cramps.

The convulsions at first are rapidly intermittent (clonic) but soon become tonic, resulting in a typical tetanus. The muscles of the diaphragm are also involved so that ultimately it becomes rigid, and this together with the tense muscles of the thorax and abdomen stops respiration. Cyanosis is therefore present, the eyes protrude with dilated pupils, and the pulse is small and tense and often cannot be detected.

The convulsion usually lasts about a minute, the muscles relax, and a condition of depression almost amounting to paralysis sets in. An interval of from ten to fifteen minutes may elapse before the next attack, which usually follows some kind of stimulation. If death does not occur during a convulsion the remissions become progressively shorter, the convulsions become weaker and paralysis more prominent.

Convulsions in the higher degrees of poisoning are induced usually by reflex stimulation such as the slamming of a door, a touch, a light, a puff of air, any voluntary movement, etc. In more serious cases the spasms are undoubtedly spontaneous, but even in this instance just as few reflex stimuli as possible should be allowed to play upon the patient. Death follows usually from failure of respiration, the heart continuing to beat for some time after cessation of breathing. On the other hand, in long-continued cases of strychnin poisoning the patient may die from the exhaustion induced by the tetanus.

The symptoms generally appear in about twenty minutes after administration of the drug, although they may be delayed for a much longer period, an hour or more. If the dose is very large, death generally occurs within two hours, although it may be delayed for many hours. Even when the patient has apparently recovered, a sudden, severe spasm may occur, terminating in death. The smallest fatal dose on record is 1/4 gr. of strychnin sulphate. On the other hand, a dose of 20 gr. has been taken with recovery.

Repetition of administration leads to increased susceptibility, rather than to tolerance; hence the possible danger of too large doses continuously administered.

At times it is difficult to differentiate strychnin tetanus from other types of tetanus, such as traumatic tetanus, spinal meningitis, epilepsy or hysteria. In traumatic tetanus there has been previous malaise and slow development and the course of the condition will establish the diagnosis. If any doubt is present, treatment for strychnin poisoning should be instituted. Fever and history will differentiate in spinal meningitis and in epilepsy consciousness is lost and the reflexes are normal. In certain cases of hysteria the diagnosis is impossible, hence such cases should also be treated as for strychnin poisoning.

Treatment of Nux Vomica Poisoning.—If the drug has been taken by mouth and prominent symptoms have not appeared, thorough lavage of the stomach should be practiced, employing a chemical antidote in the wash water or administered at short intervals. Potassium permanganate is probably the most effective (¼ teaspoonful of the crystals should be dissolved in 1 quart of warm water, carefully decanted so as not to include any crystals). Iodin (15 drops of the tincture in ½ glass of water) or tannin 1 teaspoonful in ½ glass of hot water) are also useful since they render the alkaloids insoluble. They should, however, be immediately removed. Tea and coffee are less desirable, since their content of caffein, if allowed time for absorption, acts synergistically to nux vomica.

When convulsions have already set in, quick action is demanded and the patient should be anesthetized with ether or chloroform. Anesthesia with ether and chloroform should not be continued longer than possible, since both these anesthetics tend to depress the respiration. Ether is to be preferred, since chloroform may give rise to delayed poisoning. For prolonged effect, bromids in massive doses, 15 gm. by mouth or rectum, act in a manner antagonistic to nux vomica. Paraldehyd may also be useful, since it does not depress the respiratory center. Morphin should be employed with extreme caution, owing to its marked depressant action upon the respiratory center. If necessary, artificial respiration must be given. The patient should be kept as quiet as possible.

PHYSOSTIGMIN

Physostigmin (also called eserin) is the alkaloid of Calabar bean and is usually employed either as the alkaloid, the extract or the tincture. Its chief action is that of stimulating secretory nerve endings of glands and the nerve endings of striated and smooth muscle. It causes a powerful contraction of the smooth muscle of the eye and of the intestine. It is employed in diseases of the eye and in intestinal paresis. It is antagonistic in its action to atropin.

The symptoms of poisoning by physostigmin are marked muscular weakness without loss of consciousness, nausea, vomiting and sometimes purging. The pupils are noticeably contracted, the skin is covered with sweat, there is epigastric pain, salivation, lacrimation, palpitation with slow pulse, low blood-pressure, dyspnea, muscular twitchings, and convulsions. The loss of muscular power starts in the legs and travels upwards. Respiration is depressed and the breathing may be asthmatic in character from contraction of the bronchial muscles. Death is caused by failure of respiration.

Treatment.—Lavage of the stomach, stimulants and atropin (½ to 1 mg.) is the usual treatment. Magnesium sulphate is also antagonistic to the action of physostigmin and its subcutaneous use in physostigmin poisoning has been recommended.

PICRIC ACID

At present picric acid is one of the most common therapeutic agents for the local treatment of small superficial burns. It has been advised in a number of affections of the skin—acute eczema, intertrigo, and herpes labialis. For the unbroken skin, alcoholic solutions may be used, but in superficial burns only the aqueous solutions should be employed, otherwise poisonous symptoms may arise.

Evidences of the toxic action of picric acid applied locally consist of an acute inflammation of an erythematous nature, the later appearance of vesicles and considerable local edema. The usual constitutional symptoms are headache and an annoying insomnia. Itching of the affected part is almost unendurable. Later the acute lesions involute to an erythemato-aqueous type, accompanied by considerable thickening and possibly infiltration of the skin. This stage is not unlike an eczema.

Taken internally, picric acid is probably absorbed as the sodium salt. The picric acid is in part reduced to picramic acid by the liver and other tissues of the body as a method of detoxication. Elimination is chiefly through the urine, to which an intense yellow color is imparted, or the urine may be colored a peculiar red or reddish-brown. After a single dose of a gram, the excretion of picric acid may continue for a week.

The symptoms of intoxication are referred to either the gastro-intestinal, nervous, circulatory, or urinary systems or more commonly to several of these locations. Depending on the degree of the intoxication, the gastro-intestinal symptoms vary from a mild anorexia, dyspepsia and flatulence to a severe diarrhea, accompanied by gastrodynia, abdominal cramps and emesis, the vomited matter being stained yellow. The irritant action of picric acid on the mucous membranes is responsible for the gastritis found. The nervous manifestations vary from a slight headache and vertigo to stupor with convulsions, followed by collapse in the extremely severe cases. Picric acid is a respiratory and cardiac depressant, but symptoms referable to these systems are rare. At times a primary tachycardia with a subsequent slowing of the pulse rate may be noted. Occasional symptoms are strangury and anuresis. Asthenia and fever may accompany the above constitutional manifestations of internal picric acid poisoning. Toxic doses may also destroy the red corpuscles, and induce hemorrhagic nephritis and acute hepatitis. Yellow pigmentation of the mucous membranes is usually observed and superimposed upon this may be an erythema or even a generalized eruption of eczematous character and itching in nature. This dermatitis may partake of the nature of a measles rash.

Treatment of Picric Acid Poisoning.—*Taken internally and with constitutional effects.*—Lavage of the stomach with administration of large volumes of water to hasten elimination is indicated.

Local evidences of poisoning.—The treatment to be followed is identical with that for acute eczema.

ETHER

Death from ether during anesthesia is rare. The danger signals of overdosage of ether occur suddenly and consist of pupil dilatation, pallor and a changed facial expression. Usually death in deep anesthesia is caused by respiratory paralysis with more or less involvement of the circulation. Respiration ceases even while the heart action is good.

Serious but not necessarily fatal sequelæ to ether anesthesia may be exhibited upon the respiratory organs and the kidney. Thus bronchitis, pneumonia, pulmonary edema and the flaring up of an old tuberculous lesion of the lung are some of the common after effects of ether anesthesia induced in part perhaps by the irritative properties of the ether. Albuminuria and nephritis also sometimes occur.

Treatment of Unfavorable Symptoms with Ether.—If the pulse is weak, rapid or irregular, stop anesthetic. If collapse occurs, the head should be lowered and the feet raised, giving patient free access to air. Maintain body temperature. Give hot saline by rectum or slow intravenous infusion containing 1 c.c. of epinephrin per liter. Artificial respiration should be practiced, if indicated. For stoppage of the heart, rapid rhythmic pressure over the heart or on the epigastrium should be tried.

CHLOROFORM

Chloroform anesthesia is attended by at least three sources of danger: (1) early heart failure; (2) depression of the heart with limited margin of safety; (3) delayed chloroform poisoning. In the early stages of chloroform anesthesia, the common symptoms are sudden cessation of respiration, asphyxia leading to dilatation of the heart, vagus stimulation, and finally failure of the heart because of the asphyxial condition. In light chloroform narcosis the heart muscle becomes overstimulated, sometimes inducing ventricular fibrillation, followed by death. It is probable that this type of action is due to excessive reflex inhibition of the vagus and the direct action of the chloroform upon the heart muscle, chloroform being recognized as a protoplasmic poison. Even after the heart has stopped, respiration may be resumed, but generally the heart cannot be revived. In most instances, therefore, the heart ceases before respiration and the former must be regarded as the real cause of death. When death occurs in deep anesthesia with chloroform, the blood-pressure steadily falls, respiration fails and the heart stops. Generally, however, the pulse cannot be felt before respiration ceases. Usually such accidents occur when the concentration of the chloroform vapor has been too high. Warning signs of this type of chloroform poisoning are shallow or irregular respiration, a pulse that is either very slow or very rapid, dilatation of the pupil and cyanosis.

Delayed Chloroform Poisoning.—By delayed chloroform poisoning is meant the condition which develops in some patients a few hours or days after chloroform administration and which is marked by great prostration, delirium, coma and death. The symptoms may appear suddenly or gradually. When the onset is sudden, recovery from the anesthesia has hardly been attained before the untoward symptoms appear. These consist of shrieking and struggling alternating with intervals of stupor or coma; profuse vomiting which may be blood-stained; cyanosis, jaundice, edema, renal hemorrhage, acetone breath. The urine contains albumin and casts and the ammonia coefficient may be high. The urine also usually contains acetone, diacetic and B-oxybutyric acid. The blood shows retention of non-protein nitrogen, urea and amino-acids.

Autopsy shows extensive vacuolization and fatty degeneration of the liver, swelling and necrosis of the cells, especially about the central veins. Fatty degeneration also occurs in the kidney and sometimes in the heart and arteries. Children are especially susceptible to this type of chloroform poisoning and patients with diabetes, hepatic diseases, cyclic vomiting, rickets or wasting diseases, renal disease, alcoholism and anemia are particularly likely to succumb to this condition. In general, delayed chloroform poisoning almost certainly causes death, very few cases ever having recovered.

Impurities in the anesthetic are not responsible for the untoward effects, contrary to popular opinion. They may contribute to the local irritative symptoms, but are probably not concerned in the dangerous effects. Swallowing of chloroform may cause gastritis and the phenomena characteristic of delayed chloroform poisoning.

Treatment.—Treatment of chloroform poisoning (excluding delayed chloroform poisoning) consists in stopping the anesthetic, the head being lowered, and artificial respiration being resorted to immediately. This prevents asphyxia and aids in the elimination of the poison. In order to aid the action of the heart, the cardiac region should be strongly compressed at the rate of forty times per minute. Saline solution containing 1 c.c. per liter of 1:1000 solution of epinephrin should be injected into the cardiac end of an artery. None of these measures are of value unless they can be taken immediately.

ATROPIN

Atropin is found in the plants belladonna and stramonium and may be regarded as the tropeic ester of a base, tropin, and it is isomeric with hyoscyamin. Atropin actions fall into two groups: (*a*) stimulation of nerve centers, principally cerebral and medullary; (*b*) depression of nerve endings, such as sensory nerve endings, motor nerve endings in the smooth muscle of the viscera, secretory nerve endings, the ends of the third nerve in the eye and vagus nerve endings. Poisoning may occur from administration of the isolated drug or from absorption through the skin by the use of plasters, oily or alcoholic preparations such as ointments or liniments. Toxic symptoms in ophthalmic practice are fairly common.

The first warnings of toxic action are the dilated pupil, dry throat and mild cerebral symptoms. The symptoms occur promptly but may last several hours or days. In fatal cases the course of intoxication may run for two weeks or more. With severe poisoning there may be cerebral stimulation as evinced by delirium; later this is followed by collapse and coma. Death usually occurs in coma. Convulsions at the terminal stage are rare.

During the stage of stimulation there is great thirst, burning and constriction of the throat, difficult swallowing, flushed skin, especially of face and neck, which resembles a scarlatinal rash. Accommodation of the eye is paralyzed so that vision is disordered. The pulse is rapid, respiration deep and rapid, arterial pressure is high, the temperature may rise several degrees, there is vertigo, muscular incoördination, often nausea and vomiting, and retention of urine. During the stage of delirium, patients with atropin poisoning strongly resemble maniacs, and in the earlier period of the poisoning the condition has been mistaken for scarlet fever.

After the period of stimulation collapse follows, which is characterized by feeble heart action, low blood-pressure, a slow and shallow respiration, coldness of the extremities, death resulting usually from respiratory failure.

The autopsy reveals findings typical of asphyxia.

Treatment.—Treatment of atropin poisoning is quite effective since death does not usually occur rapidly, and it consists of lavage of the stomach, tannic acid or tea being added to the wash water. The general symptoms should be combated by pilocarpin, 10 mg. (1/6 gr.) subcutaneously repeated until the mouth is moist. For the delirium, bromids and the ice-cap are indicated. Because of their depressant effect upon the respiratory center, morphin, chloral and chloroform should not be used, although the cautious use of morphin in the early excitement may be beneficial, or ether may be inhaled to lessen excitement. In the stage of collapse depression should be antagonized by strong coffee and artificial respiration persistently resorted to, if necessary.

PILOCARPIN

Pilocarpin is the principal alkaloid of jaborandi leaves and it is distinctly antagonistic to the action of atropin peripherally stimulating the secretory nerves, the nerves governing smooth muscle, etc. The principal secretion affected is the sweat, pilocarpin being a powerful diaphoretic. The preparations commonly employed are pilocarpin the alkaloid, the fluid extract, the hydrochlorid and the nitrate.

Although the toxicology of pilocarpin is not very important, cases of poisoning from overdoses occasionally occur. After toxic doses, pilocarpin is an arterial dilator; it acts as a cardiac depressant, both from the action on the vagus and from its direct influence on the heart; in conditions of cardiac weakness, collapse and death may follow even from relatively small doses; respiration is also depressed, leading to pulmonary edema and asphyxia.

The symptoms of poisoning resemble those of muscarin and start with greatly increased secretion of saliva, sweat and tears. This may be followed by nausea, vomiting and diarrhea with severe abdominal cramps. Changes in the eye are quite noteworthy, there being contraction of the pupil and spasm of accommodation. There is at first slowed heart beat, low blood-pressure, and later collapse. These symptoms are due to the action of pilocarpin upon the vagus and upon the vasomotor center, resulting respectively in vagus heart block and low pressure. Respiration is usually labored and of the asthmatic type and the lungs may give evidence of edema. Muscular relaxation which ascends from the lower limbs sometimes occurs. Generally consciousness is present, although there may be confusion of ideas, vertigo, tremors, and feeble convulsions. Death results from paralysis of the heart or from pulmonary edema.

Less dangerous symptoms of overdoses of pilocarpin manifest themselves by gastro-intestinal disturbances, nausea, and vomiting which may be long continued and very depressing. These symptoms may occur even though the drug is not introduced by mouth. Another characteristic symptom is a burning sensation in the urethra accompanied by an irresistible desire to urinate.

Treatment.—Treatment for pilocarpin poisoning consists in the use of atropin to combat the pilocarpin effects and symptomatic treatment, especially artificial respiration for the collapsed state. The atropin tends to lessen bronchial secretion, hence prevent edema, modifies the asthmatic respiration and abdominal cramps and counteracts the pilocarpin action upon the vagus, thus releasing the heart from its block.

NITRITES

The nitrite group of drugs includes the inorganic nitrites, the nitrous esters, such as amyl nitrite, ethyl nitrite or "sweet spirit of niter," and those nitrates which are reduced to nitrites in the body. Nitroglycerin is the most important member of this group.

Although death rarely, if ever, occurs after the therapeutic use of the nitrites, it is quite common for untoward symptoms to appear which, however, usually pass over rapidly. The effects seem to be aggravated if the patient is in an upright position.

Symptoms.—The symptoms most obvious are a pounding heart, flushing of the face and neck, throbbing and fullness of the head "as if the top of the head were coming off," and intense headache. There may also be confusion of ideas, visual disturbances, dizziness, a feeling of faintness, or indeed actual fainting may occur. At times there may be localized edema and excessive sweating. The symptoms are probably referable to low cerebral blood-pressure.

There is a wide range of susceptibility to the action of the nitrites, some patients displaying marked toxic symptoms with very small doses, others being unaffected with very great quantities.

In general the nitrites in large doses form methemoglobin which produces cyanosis and asphyxia. Excessive doses of nitroglycerin may produce nausea, vomiting, colic, and at times bloody diarrhea. There is a flushed and perspiring skin; headache is persistent; vertigo is present; and very rarely blindness and delirium. Respiration is markedly altered, hyperpnea at first obtaining, being followed by dyspnea. The body surface is cold with cyanosis, the heart is slowed, paralysis occurs, convulsions appear and death results within seven or eight hours from respiratory failure.

Nitrite poisoning may also occur from the administration of bismuth subnitrate (see Bismuth Subnitrate).

ACONITE

Aconitum or monk's hood contains several alkaloids of which aconitin is chief. Its principal therapeutic effects are upon the circulation, producing slowing of the pulse and fall of pressure. Employed locally as the tincture it has value for the relief of pain in toothache, neuralgia and rheumatic conditions. The principal preparations are aconitum U.S.P. containing not less than 0.5 per cent of alkaloids; the extract representing 2 per cent of alkaloids, the fluid extract containing 0.5 per cent of alkaloids, and the tincture 10 per cent of drug or 0.05 per cent of alkaloids. A characteristic action of aconite is the tingling sensation in the mouth which is followed by numbness and loss of sensation. This action is produced locally wherever the drug may be applied.

Symptoms of poisoning consist in tingling in the mouth, stomach and skin, and may be most pronounced in the finger tips. This characteristic feature is of considerable importance in the diagnosis of aconite poisoning. There may be nausea, diarrhea, vomiting and pain in the stomach. The burning and tingling sensations pass into anesthesia. There are peculiar chilly sensations, the pupils are dilated and vision is misty, the skin is cold and pallid, respiration is dyspneic, the pulse is weak and feeble and arhythmic. Speech may be impaired and convulsions are not infrequently encountered. Death occurs from respiratory failure or from heart block, or ventricular fibrillation.

When large doses are taken, death may result very rapidly from heart paralysis.

Treatment.—Treatment of aconite poisoning demands prompt administration of alkaloidal antidotes, emptying of the stomach and lavage. Body temperature must be maintained and artificial respiration may be necessary. The heart condition may be treated by epinephrin or strophanthin injected directly into the circulation. Atropin is of great value in aconite poisoning to counteract the heart and respiratory disturbance.

VERATRUM VIRIDE

Veratrum viride, or green hellebore, a tall herb growing in wet regions of North America, contains a number of related alkaloids, chief of which is protoveratrin. Its chief action is that of a cardiac depressant from vagus stimulation, resulting in slowed pulse, fall of blood-pressure and reduction of temperature, the latter probably from the profuse sweating produced. Veratrum has been employed therapeutically to slow and soften the pulse and lower blood-pressure. It has enjoyed a wide use in conditions of high blood-pressure, particularly that associated with eclampsia. The preparations most employed are Veratrum viride, the fluid extract, and the tincture.

Death from overdoses of Veratrum viride is rare, owing to the fact that it is a strong gastric irritant and promptly causes vomiting. On the other hand, fatal cases have been reported, the symptoms consisting of gastro-intestinal irritation as evidenced by vomiting and diarrhea, irregularity of the heart from vagus stimulation, cardiac exhaustion, collapse, paralysis or convulsions. Death is caused by paralysis of the respiratory center with accompanying heart failure.

Treatment.—The treatment of poisoning by Veratrum viride consists in evacuation and lavage of the stomach and the collapse treated by stimulants such as warmth, ammonia, brandy, atropin, strychnin.

VERATRIN (CEVADIN)

Veratrin is a mixture of alkaloids extracted from cevadilla seeds. Its principal constituent is cevadin. Veratrin has been employed therapeutically in the form of an ointment as a counter irritant in neuralgic conditions, especially of the face. Being highly toxic, its internal administration is not advised and poisoning has occurred from absorption through the skin.

Toxic symptoms provoked are gastro-intestinal disturbance, such as burning in the stomach, vomiting, diarrhea, abdominal pain; increased salivation; giddiness, headache, dilated pupils; irregular heart action; collapse and death from respiratory failure and collapse of the circulation. Autopsy sometimes reveals ecchymoses in the intestines.

Treatment.—The treatment of veratrin poisoning consists in the employment of alkaloidal antidotes, emptying and lavage of the stomach. Stimulants, such as ammonia, brandy, atropin and warmth should be administered. Artificial respiration is of great value when indicated, and the heart may be helped by intravenous injection of epinephrin or strophanthin, should the need arise.

CONIUM

Conium, or "poison hemlock," is a plant growing wild in various parts of the United States. It closely resembles parsley and from this cases of poisoning have occurred. Coniin, a volatile alkaloid, is the active constituent of this plant and is a derivative of pyridin. The fluid extract, dose 3 minims (0.13 c.c.), is official but at present is not employed to any extent. Formerly it was used as a sedative and antispasmodic. The concentrated free alkaloid is a local caustic.

Poisonous action comes on very rapidly, the symptoms consisting of pain in the head, faintness, lassitude, muscular weakness and pupil dilatation; the intellect remains clear, paralysis of the extremities takes place, and death occurs from respiratory failure.

Treatment.—The treatment of conium poisoning consists in lavage of the stomach, employing tannin as an antidote, stimulation, and maintenance of the respiration.

GELSEMIUM

Obtained from the rhizome and roots of Gelsemium sempervirens, the yellow jasmine, the alkaloid gelseminin, acts in a manner somewhat similar to nicotin and coniin, although its action upon the central nervous system is more depressing. Another alkaloid found in company with gelseminin is gelsemin, which has a weak strychnin influence. Official preparations are fluid extract (dose 1 minim, 0.06 c.c.) and the 10 per cent tincture (dose 10 minims, 0.6 c.c.). Although it has been employed therapeutically in neuralgias, the mechanism of its action is not understood.

Relatively small doses may cause toxic symptoms and even death. A dram of the fluid extract has caused death and 15 minims have provoked evidences of poisoning. The symptoms consist of double vision, relaxation of the muscles of the eye and jaw, general muscular relaxation and weakness, great prostration. The respiration at first is accelerated, later becoming slow and shallow. The mind remains clear and death results from respiratory failure.

Treatment.—The treatment of gelsemium poisoning consists in lavage of the stomach, atropin and stimulants.

THYMOL

Thymol is allied to the creosote constituents and in its action resembles phenol. Contained in a number of aromatic oils, for example, thyme, it has high antiseptic value, low germicidal properties and relatively low toxicity. It is employed chiefly as an anthelmintic in the treatment of hookworm disease. In about one-half the cases treated, unfavorable symptoms are observable and in rare instances severe poisoning occurs and even death. The symptoms resemble those of phenol, except that convulsions do not occur, the chief action being depression of the central nervous system. In therapeutic use alcohol or oily solutions or mixtures should be avoided, since toxicity is greatly favored, owing to the more rapid absorption of the dissolved thymol.

Treatment.—The treatment consists of emptying the stomach, lavage, saline cathartics (not castor oil) and stimulants for the central nervous system.

BENZENE POISONING

Benzene has come into prominence as a symptomatic remedy in the treatment of leukemia. At times it apparently causes considerable improvement in this disease, but the results of its use are not reliable and indeed are sometimes dangerous. The symptoms arising from its medicinal use are heart-burn, flatulence, nausea, vomiting, diarrhea, bronchial irritation, minute hemorrhages of skin and mucous membranes (purpura hæmorrhagica) albuminuria, ringing in the ears and vertigo. Liver, kidney and intestinal disturbances contra-indicate benzene.

If after administration of benzene the leukocytes show a rapid fall in number, the benzene should be stopped at once, no matter how high the count, for this is an indication of severe aplasia, otherwise the leukocytes will continue to fall with fatal results. Under the circumstances, the bone marrow is very red with myelocytes and much new connective tissue, new vessels and hemorrhages.

Treatment.—This is purely symptomatic in the milder forms, but in the stage of continued leukocyte destruction and the accompanying anemia repeated transfusion of blood seems essential in order to save life.

CUBEBS AND COPAIBA

The oleoresins of copaiba and cubebs are employed as urinary antiseptics in subacute and chronic urethritis. They are used as aids to local treatment to diminish pain and the discharge and to hasten healing. Cubebs are also sometimes used in bronchitis. The oleoresins are rich in terpenes and resin acids which are mildly irritant. This irritant action is induced along the urinary tract as a stimulus to repair, the terpenes at the same time acting as antiseptics.

These substances are also irritating to the gastro-intestinal tract, causing anorexia, colic, eructations and diarrhea. Scarlatinal rashes occur in some patients, whether from the direct action of the drugs or secondary to the gastro-intestinal disturbance is uncertain. With large doses there is intense irritation of the urinary tract, resulting in renal pain and albuminuria.

CITRATES

From the toxicological point of view, the citrates are of little importance since given by mouth they are harmless, even in large quantities. Since 1915, when Weil suggested the use of sodium citrate to prevent blood coagulation during transfusion, there have been numerous cases showing untoward symptoms which, although not dangerous or of much practical significance, are nevertheless sufficiently outstanding to be worthy of note. The symptoms consist of fairly severe chill and fever of 2.5°F. in about one-half hour subsequent to transfusion of citrated blood; but within from four to eight hours normal conditions are restored.

Varied views have been held relative to the cause for such symptoms and perhaps the most likely hypothesis is that the corpuscles and platelets are changed or injured by the citrate withdrawing calcium from the blood elements and combining with it to form a stable compound.

SALICYLATES

Because of their close relationship to phenol, one might suspect the salicylates of possessing toxic properties. In general the early evidences of toxicity are nausea, vomiting and sometimes diarrhea, or headache, ringing in the ears, and deafness or mental excitement.

Salicylism resembles cinchonism, although the ear symptoms are not as common as with quinin. These may be due to either congestion or anemia or to changes in the nervous tissue of the cochlea. Disordered vision may also occur, which is associated with degenerative changes in the retina or optic nerve. Other characteristic symptoms are a feeling of fullness of the head, angioneurotic swelling of the face and throat, general urticaria, mental dulness and apathy, muscular weakness, or mental excitement with loquacity, a talkative delirium, the so-called "salicylic jag," the cerebral symptoms of which resemble those of atropin. Alcoholics are especially susceptible to this type of reaction.

With very large doses, or because of idiosyncrasy, there may be weakening of the heart and depression of respiratory and vasomotor centers followed by collapse. Hanzlik asserts that, even with full therapeutic doses, albumin, leukocytes and casts appear in the urine of both normal individuals and rheumatic patients. The administration of bicarbonate with the salicylate has practically no demonstrable influence upon the albuminuria and renal functional changes produced by the salicylate. This evidence of inflammation of the kidney promptly ceases upon stopping administration of the drug. With full therapeutic doses there may be diminution of the urine with corresponding increase of body weight due to fluid retention in the tissues. Although edema is not visible, this is probably an edemic condition.

All toxic effects of salicylates are usually without danger, disappearing as soon as the drug is stopped. On the other hand, a few deaths have been reported from large doses or because of idiosyncrasy. It is, however, difficult to determine whether death in these cases was induced by the drug or whether the accompanying disease was responsible. Autopsy findings in these instances show hyperemia of the brain and its membranes, of the kidneys and lungs and ecchymoses of the pericardium.

In a clinical statistical study of the toxicity of different salicylates in adult males and females, respectively, Hanzlik found the toxic dose to be as follows: 180 and 140 gr. of the synthetic salicylates; 200 and 135 gr. of the natural sodium salicylate; 120 minims of the methyl salicylate; 165 and 120 gr. of acetyl salicylate; 100 and 83 gr. of salicylo-salicylic acid. For females the toxic dose was approximately 80 per cent of that for males. The toxic dose of the different salicylates was uninfluenced by age between sixteen and seventy-five years, by racial differences, various diseased conditions, and therapeutic response with the synthetic salicylate. Individuals showed idiosyncrasy toward toxic doses of the synthetic salicylate, but no relationship was found to exist between this and such factors as age, race and diseased condition. Idiosyncrasy varied in the same patient, and was not influenced by previous salicylate medication. The toxic dose for children is higher than would be calculated for the age.

Treatment.—The drug should be stopped. Usually the symptoms quickly disappear. Bromids control, in a measure at least, the cerebral excitement. Renal excretion is stimulated best by large volumes of water.

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CHAPTER XLI

POISONING BY WARFARE GASES

Harry L. Gilchrist

Much has been written about the horrors of gas warfare and the diabolically cruel consequences resulting from its use. But after a close analysis of the casualties produced in the War and the mortalities following, it is an incontestable fact that the ratio of deaths and permanently injured from this weapon to the total number of casualties produced by other weapons is an index of its humaneness.

History shows that as the methods used in a war have progressed in efficiency as a result of the application of scientific discoveries, the death-rate has constantly decreased. Gas is the latest contribution to the science of war and both experiences and statistics of the World War show that it is not only one of the most efficient agencies for effecting casualties, but the most humane method of warfare ever used on the battlefield.

According to the report of the Surgeon-General of the Army for 1920, 260,783 men were injured during the war. Of these 34,249 died on the field of battle and 13,691 died in hospitals. There were admitted to the hospitals, exclusive of marines, 224,089 patients, of which number 70,552 or 31 per cent were suffering from gas alone. (See Fig. I.) Of this number only 1,221 died. Of the 153,537 admitted to the hospitals suffering from bullets, high explosives, and other methods of war exclusive of gas, 12,470 died. Of those killed on the field of battle, not over 200 were from gas, since concentrations of gas sufficient to kill within twelve hours were seldom obtained. If it is assumed that 200 died from gas on the field of battle, the total deaths from gas would be 1,441 out of 70,552, or 2.04 per cent. In like manner, of the 187,586 injured by bullets, high explosives and similar methods, 46,449 or more than 24 per cent died. Thus it is evident that the man who was injured by gas alone on the field of battle had twelve times as many chances for recovery as the man wounded with bullets and high explosives. If as many had died from gas as high explosives and bullets, there would have been 15,500 more dead and about 3,000 more crippled.

Other comparisons are still more striking. On page 21 of that report it appears that 66 men were totally blinded in the war, 44 were partially blinded in both eyes, and 644 were blinded in one eye. These include eyes destroyed or those in which the sight was lost. Of the gassed patients, it is stated that 4 were blinded in both eyes and 29 in one eye, a total of 33. These 33 were 4.3 per cent of all those suffering blindness in one or both eyes. In other words, bullets and high explosives, and other methods of warfare than gas, were responsible for twenty-five times as many blinded as was gas. In addition, bullets, etc., were the cause of the loss of one or more parts of the extremities (legs and arms) of 4,403 soldiers, while 4,790 had the flexibility of one or more joints totally or partially destroyed.

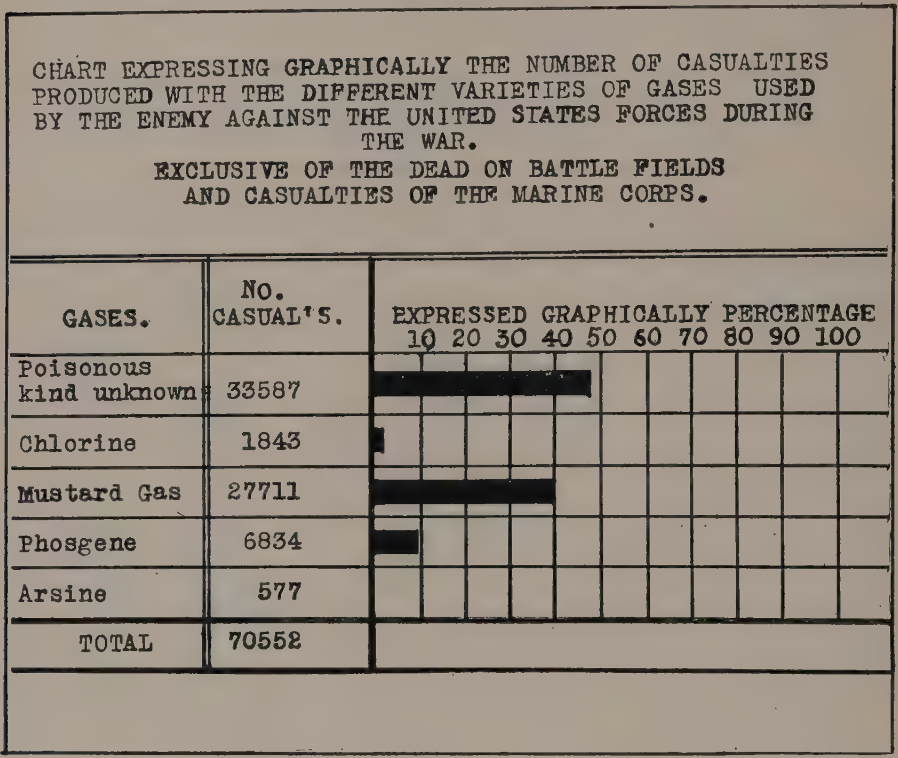

CHART EXPRESSING GRAPHICALLY THE NUMBER OF CASUALTIES PRODUCED WITH THE DIFFERENT VARIETIES OF GASES USED BY THE ENEMY AGAINST THE UNITED STATES FORCES DURING THE WAR.
EXCLUSIVE OF THE DEAD ON BATTLE FIELDS AND CASUALTIES OF THE MARINE CORPS.

GASES.	NO. CASUAL'S.	EXPRESSED GRAPHICALLY PERCENTAGE 10 20 30 40 50 60 70 80 90 100
Poisonous kind unknown	33587	
Chlorine	1843	
Mustard Gas	27711	
Phosgene	6834	
Arsine	577	
TOTAL	70552	

Fig. 1.—Graphic Chart Taken From the Official Report of Colonel Gilchrist, Chief of the Medical Division, Chemical Warfare Service, U. S. A., 1922.

CHEMICAL AGENTS USED IN GAS WARFARE, AND THEIR CHEMICAL PROPERTIES

The term "gas" is used to denote any of the several chemical agents used in combat, whether gases, liquids or solids. The term "chemical agent" includes all chemicals and chemical compounds, whether gases, liquids or solids, used against personnel, and dependent primarily for effectiveness on direct chemical activity. Chemical agents differ materially from other projections against the enemy, in that they are not dependent on momentum or disruptive force for effect but on direct chemical action.

The several chemical agents fall into the following classifications:

Gases.
Liquids.
Solids.

This classification is based upon their physical condition at ordinary temperatures and pressures.

Upon these qualities depend to a material extent the several methods of projection; for example, gases such as chlorin, which exert a relatively high vapor pressure, can be liberated from cylinders forming gas clouds which are carried along by the wind, while liquid agents such as mustard must be dispersed by an explosive charge sufficient to cause atomization and effective vaporization. Other liquids of different characteristics require different degrees of explosive force to produce dispersion.

Solids can be effectively dispersed by an explosive charge completely pulverizing the agent. These same agents also can be effectively put over by volatilization, due to the heat-generating mixture of the so-called candle.

Gases may be divided according to their physical properties into (1) persistent, and (2) non-persistent gases.

1. Persistent gases include all chemical agents, which, after projection, remain on the ground giving off vapor in effective or dangerous concentrations for long periods. There is a large variation in duration of effective concentrations in this class, depending upon the agents used; the time may vary from a few minutes to several weeks.

2. Non-persistent gases include chemical agents which produce their effect in a very short space of time. The terrain is cleared of these agents rapidly by the wind. They are gases or smokes and do not settle or condense on the ground in effective concentrations.

The principal chemical agents, together with their code designations, are:

Chlorin
CG—Phosgene
PS—Chlorpicrin
BA—Bromacetone
CA—Brombenzylcyanid
CN—Chloracetophenone

DA—Diphenylchlorarsin
DM—Diphenylaminechlorarsin
HS—Dichlordiethylsulphid—Mustard
M—Chlorvinyldichlorarsin—Lewisite
WP—White Phosphorus
FM—Titanium Tetrachlorid

Other chemical agents are:

H. C.—Smoke Mixture
Thermit Mixtures
Spontaneously inflammable oil.

Chlorin.—Chlorin is a heavy yellowish-green gas possessing a typical and disagreeable odor. The vapor density of chlorin as compared with air is 2.49. Being about two and one-half times as heavy as air it is especially suited for cloud gas attacks. The gas when released from cylinders lies close to the ground and is carried along by the wind as a thick, suffocating and deadly cloud enveloping everything within its path. Chlorin boils at —33.6° C.; its vapor pressure at 20° C. is 4,993 mm. of Hg., or 6.62 atmospheres.

Chemical Properties.—The natural compounds of chlorin are chlorids of metals. Its principal sources are the large salt deposits found throughout the world. The gas is composed of two atoms of chlorin, its chemical formula being Cl_2. It is an important element in the manufacture of a number of other compounds used in chemical warfare; for instance, it is used in the manufacture of M, CN, CG, PS, DA, DM and HS. Chlorin is soluble in water. It is manufactured by electrolysis of common salt: $2NaCl = 2Na + Cl_2$.

CG—Phosgene.—CG is considered second only to HS in general value. It is the most effective lung irritant and lethal agency known.

It is a clear, colorless, mobile liquid; above boiling point (8.2° C) it is a gas. It freezes at —75° C. It is characterized by an odor, depending somewhat on concentration, variously described as of musty hay or green corn. Its vapor density compared with air is 3.5; its vapor pressure at 20° C. 1,175 mm. of Hg.

This agent is used largely in shells and bombs, and is also effective from cylinders in cloud attack. Due to its fairly high boiling point and low vapor pressure as compared with gases such as chlorin, it is, when used from cylinders, mixed with some gas of lower boiling point and higher vapor pressure, such as chlorin or carbon dioxid, thus effecting more ready liberation.

Chemical Properties.—Phosgene or carbonyl chlorid is a chemical compound manufactured from carbon monoxid and chlorin, the reaction being $CO + Cl_2 = COCl_2$. It is a fairly stable compound at ordinary temperatures and in the absence of moisture. It is, however, very readily hydrolyzed in the presence of water or water vapor, and is consequently rapidly destroyed in moist or rainy weather. It has no action on metals when dry, but in the presence of moisture vigorously attacks iron, steel, brass and other common metals. It is readily destroyed by alkalis, steam or hot water.

PS—Chlorpicrin.—Chlorpicrin is a slightly yellow, slightly oily liquid between —69.2° C., its freezing point, and 112° C., its boiling point. It has a characteristic pungent odor, but in the field is first detected by its irritating effect on the eyes. Its vapor density compared with air is 5.70; its vapor pressure at 20° C. is 19.20 mm. of Hg. Effective volatilization and diffusion depend upon dispersion by explosives or some mechanical means of atomization.

Chemical Properties.—PS is chemically a fairly stable compound; it is unaffected generally by mineral acids; it is readily decomposed by 50 per cent alcoholic sodium sulphite. It is, chemically, nitrotrichloromethane or nitrochloroform, has the constitutional formula CCl_3NO_2 and is manufactured from picric acid and bleaching powder. It reacts very slightly with common metals, producing merely a slight tarnish.

BA—Bromacetone.—BA is at present regarded as obsolete and is included here only because of its historical interest. It was favored in the late War as a lacrimator. It possesses the inherent defect of being unstable in storage, decomposing readily to a thick, viscous, black mass. Pure BA is a colorless liquid, but as prepared commercially it varies from yellow to brown. Its boiling point is approximately 126° C., at which temperature it decomposes. Its chemical formula is CH_3COCH_2Br and it is prepared by direct bromination of acetone.

CA—Brombenzylcyanid.—CA is one of the most effective lacrimators developed. When pure it is a yellowish-white crystalline solid melting at 24.8° C., but as prepared commercially is a dark brown, oily liquid; its boiling point is 242° C.; its vapor density compared with air is 6.77. Its dispersion in the War was effected from shells and bombs by an explosive charge, but other methods of dispersion are under consideration and experiment.

Chemical Properties.—It is insoluble in water but is soluble in and readily miscible with several other chemical agents, including CG and PS, and effective results have been obtained by using small amounts in phosgene-filled shell for producing lacrimation. It rapidly attacks all metals except lead. C-A filled shell must, therefore, be lined with either lead or other material chemically inert with reference to this agent.

Under ordinary conditions CA is a liquid. It is highly persistent and has, in cold weather, remained on the ground in effective lacrimatory concentrations as long as thirty days. Physiologically, in high concentrations, it produces an irritant effect on the respiratory tract, but in concentrations practically obtainable in the field this effect is negligible.

CN—Chloracetophenone.—CN appears as white crystals at ordinary temperatures, its melting point being 58° C. Its vapor density compared with air is 5.33; its boiling point is 247° C.; its vapor pressure at 20° C. is 0.013. It is not decomposed by boiling and can be melted and poured into shell or other containers, its specific gravity as a solid being a little less than pressed TNT. Meteorological conditions materially affect this agent. In warm weather it is highly effective, but in very cold weather vaporization is almost entirely suspended, with consequent loss of effect.

Chemical Properties.—CN is soluble in a number of chemical agents and several organic solvents. It does not attack metals. This compound is, as its name indicates, a halogen derivative of an aromatic ketone, its formula being $C_6H_5COCH_2Cl$. It is manufactured by the chlorination of acetic acid to obtain monochloracetic acid and the chlorination of this compound to obtain chloracetylchlorid, which reacts with benzene in the presence of anhydrous aluminum chlorid to give chloracetophenone.

It is a highly persistent gas. Physiologically, it is highly lacrimatory in minute concentrations.

DA—Diphenylchlorarsin and DM—Diphenylaminochlorarsin.—These substances are similar in their principal characteristics, and produce their effect not by the formation of vapor but by means of very minutely divided solid particles which are liberated in the air, forming so-called toxic smokes. They are both characterized by extremely high boiling points and correspondingly low or almost negligible vapor pressures.

Classification.—Under ordinary conditions these substances are solids. In sufficient concentration they are toxic and produce casualty effects which require time for treatment and recuperation; based upon time element they may be considered non-persistent, being carried along by the wind and dissipated, although a sufficient amount of either may settle on trees and undergrowth to be noticeable by troops which promptly follow up their liberation. Physiologically, these substances produce both a distinct toxic effect as a result of absorption of toxic elements in the respiratory tract and lungs, and a marked sternutatory effect.

HS—Dichlordiethylsulphide—Mustard.—HS is a heavy, oily liquid which, as commercially produced, is dark brown and in low concentrations has an odor strongly suggesting garlic or onions. The liquid boils at about 219° C.; its vapor pressure at 20° C. is .11 mm. of Hg.; its vapor density as compared with air is 5.50. On account of the low vapor pressure HS is volatilized in the field with difficulty, so that best results are obtained by effecting a high degree of atomization by means of an explosive-bursting charge contained in the booster of shell, bombs or other containers.

Chemical Properties.—At ordinary temperatures HS is rather a stable compound. In contact with water it is slowly hydrolyzed, hence ground which has been subjected to an HS attack is rendered harmless by hydrolytic action of rain; but this action is slow, and contaminated ground is unsafe for from one to several days. This compound is readily soluble in various hydrocarbons and other organic solvents such as petroleum products, carbon disulphid, etc., and rapidly destroyed by chlorid of lime. Dichlordiethylsulphid $(ClCh_2CH)_2$ S, was first prepared twenty-five or thirty years before the beginning of the late War, but was of no practical value and almost unknown until its value as a chemical weapon in warfare was developed.

The Germans, who first used the substance in war, prepared it by the treatment of ethylene chlorhydrin, $ClCh_2CH_2OH$, with sodium sulphid, Na_2S, treating the thiodiglycol, $(HOCH_2CH_2)_2S$, thus formed with hydrochloric acid, which reacted to form dichlordiethylsulphid and water. A different and much-improved process of manufacture has now been developed.

Dichlordiethylsulphid exists between rather low and extremely high temperatures, and as to physical state it is classed as a liquid.

Physiologically it is classed as the most effective and powerful vesicant known.

M—Chlorvinyldichlorarsin—Lewisite.—This is often referred to as "the dew of death." Between the temperatures of —18.2° C., its melting point, and 190° C., its boiling point, it exists as a liquid; its vapor density compared with atmospheric air is 5.49 and its vapor pressure at 20° C. is 0.395.

Chemical Properties.—Lewisite, or chemically β chlorvinyldichlorarsin, $ClCH{:}CHAsCl_2$, is the result of the reaction occurring when acetylene, C_2H_2, is passed through arsenic trichlorid, $AsCl_3$, in the presence of aluminum chlorid, $AlCl_3$. Apparently the $AlCl_3$ does not act specifically as a catalyzer, but all three substances unite to form unstable products which decompose slowly with evolution of heat at ordinary temperatures and, when heated, with almost explosive violence, resulting in three compounds of acetylene and arsenic trichlorid, as follows: β Chlorvinyldichlorarsin—$ClCH{:}CHAsCl_2$—Lewisite—M_1: β β_1 Dichlordivinylchlorarsin—$ClCH{:}CH)_2$. AsCl—M_2: β β' β'' Trichlortrivinylarsin—$(ClCH{:}CH)_3As$—M_3.

Thus far it has been impossible to produce Lewisite without the other compounds. M_1 is a powerful vesicant, its virulence in this respect approaching mustard. It is also a respiratory irritant; M_2 compound possesses the same vesicant characteristics in a milder degree, but is a more powerful lung irritant; its odor is pungent and disagreeable, and it produces a marked sternutatory effect. Lewisite is soluble in alcohol, benzene, kerosene, olive oil and liquid petroleum. It is hydrolyzed by water and destroyed readily by chlorid of lime. It produces no effect on metals but in the presence of iron is slowly changed to M_2 and M_3, the iron apparently acting as a catalyzer.

PROTECTION AGAINST GASES

During the first gas attack in the War, the troops were caught unawares without any standard protection. In the emergency they used anything they could improvise for the occasion—blouses, shirts, handkerchiefs, socks and different materials were brought into play. These were wet with urine or some other liquid and placed over their mouths and nostrils. As a result of these ingenious arrangements thousands of lives were saved.

The first protective apparatus furnished the troops consisted of pads moistened with sodium thiosulphate, and each soldier was provided with a small bottle of the liquid, which formed part of his equipment. The next development in protective apparatus was the result of observations made in experimenting with the effects of gas upon animals. It was observed that the pig, when exposed to high concentrations of the poisonous gases for relatively long periods of time, did not suffer from the effects of the gases. It was observed that with the introduction of the gas the pig burrowed into the wet soil, through which he breathed. This led to the bottle respirator, which consisted of nothing more or less than an ordinary wine bottle with the bottom knocked off which was filled with moist earth. When exposed to gas, the men put the neck of the bottle to their mouths, held their noses, and breathed through the moistened earth.

Following this method of protection, the waterproof wallets were introduced. These consisted of pads of cloth saturated with a sodium hyposulphite solution and provided with straps for securing over the faces.

The bag helmet was the next stride, which was later supplemented by the goggles and the goggle-helmet, or the so-called P.H.G. helmet. "P" stands for sodium phenolate, "H" for hexamethylenetetramine and "G," for goggles.

Following this was the introduction of the gas mask whose improvement has kept pace with the development of gas as a weapon. From the beginning the principle of the mask has been to provide a filter through which the inspired air should pass. The filter was made of a chemical, to neutralize the gases. At first the mask was simply a pad of cloth moistened in soda solution, and this afforded fairly good protection against chlorin and the lacrimators and slightly poisonous gases. However, with the introduction of more powerful gases this type proved inadequate and as a result the box respirator mask was introduced.

The box respirator offers absolute protection to life against the greatest variety of gases. The mask used by the American forces during the War was of the British type. It consisted of a face-piece, connected by rubber tubing with a canister containing chemicals. This mask was very uncomfortable for the reason that when in use the nostrils were closed by a clip. With the use of a rubber mouthpiece connected with the rubber tubing attached to the canister it was possible to inhale through this tube the medicated air coming through the canister.

Shortly after the War an improved mask was made by the Americans without the disagreeable attachments (nose-clip and mouthpiece). This mask has been further improved and is now known as the model 1919 mask which is greatly superior to any one yet devised.

This mask retains all the advantages over former types without their disadvantages. It consists of three parts: the canister, the corrugated rubber tube and the face-piece. The canister purifies inhaled air by filtering out or chemically destroying toxic vapors or solids. In the case of smoke and toxic solids, the filtration is mechanical and it is accomplished by means of a special filter. The canister has two rubber check valves in the top for the entrance of unpurified air; after the incoming air has passed through the canister, it passes out through a nozzle located between the check valves and into a corrugated tube which conducts the purified air to the face-piece; the corrugations in the tube prevent its collapse and the consequent shutting off of air.

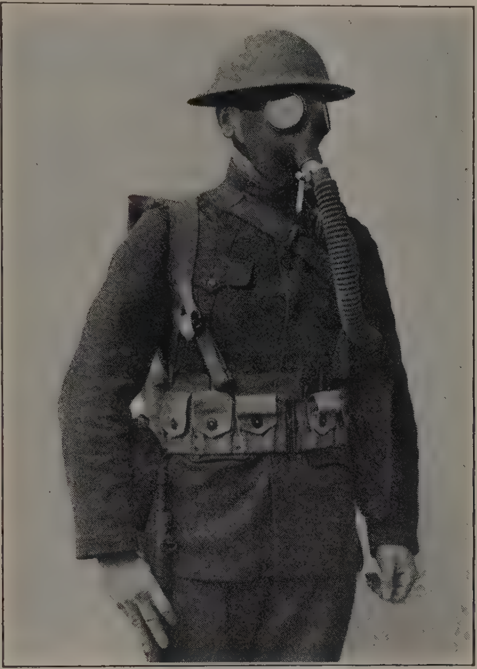

Fig. 2.—American Soldier in Heavy Marching Order Wearing the Latest Box Respirator Mask.

The fabric of the face-piece is made of a special rubber compound covered with stockinet; eye-pieces of non-shattering triplex glass lenses are inserted to allow proper vision; the face-piece is held in place by an elastic head harness. Connected with the face-piece is the angle tube, the upper part of which is for the passage of the inhaled air from the canister, the lower for the exit of the exhaled air. On the inside of the upper passage is attached a rubber butterfly-shaped deflector, the upper corners of which are cemented to the face-piece, thus causing the air to pass up and across the inner surface of the eye-pieces which prevents condensation of moisture therein. On the outside of the lower passages of the angle tube is attached a rubber flutter valve which permits exhalation but prevents inhalation.

The face-piece of the mask is made in several sizes.

The mask is carried in a canvas satchel of which there are two types of satchel now in use, known as the side satchel and the two-position satchel.

The face-piece is secured to the face by means of rubber bands. See Fig. No. 2.

The canister consists of an oval-shaped tin enclosure 7¾ inches high by 4¾ inches wide and 3 inches thick. It contains a core made of felt which acts as a filter for smokes and solids and certain chemical agents which either absorb or neutralize all toxic substances.

Protective clothing.—Impregnated clothing has been developed which protects the body against chemical agents of the vesicant gas variety. There are two general types, mechanical and chemical. The mechanical type consists of a specially treated cloth and is impermeable both to chemical agents and to air. However, clothing made from this material is stiff, hot, uncomfortable and much like oilcloth, and unsuitable for general wear, but, boots and gloves of this material have proven to be satisfactory. The second or chemical type consists of ordinary clothing or underclothing impregnated with chemicals which destroy war gases. This type can be worn continuously without discomfort or lessening of efficiency to the wearer, the objection to this method being the necessity for the constant renewal of chemicals.

Protective salves.—Several different salves have been prepared for this purpose but all are unsatisfactory.

Collective Protection Against Gases

This method of protection applies to groups instead of individuals. The measures of collective protection against gases include gasproof shelters, alarm devices, chemicals for destroying chemical agents, mobile bathing units and protective covers or containers for foods.

Gasproof Shelter.—A gasproof shelter is any enclosed space rendered gas-proof. The protection of dugouts, huts or tents against chemical agents has proved of value, especially against gases of high persistency which require the constant wearing of the respirator for long periods. The entrances to shelters are rendered gasproof by the use of double curtains of gasproof material with a space of six feet between them; the outer curtain or door slanting toward the inner one, the inner one slanting in the opposite direction thus forming a gas lock.

SOME OF THE CAUSES OF GAS CASUALTIES IN THE AMERICAN ARMY

Chief among these may be mentioned the following:

1. Arrival of new and inexperienced troops in the lines.
2. Gas attacks successfully launched as a surprise.

3. Lack of knowledge of gas odors.
4. Late adjustment of the mask.
5. Premature removal of the mask.
6. Injury to the mask.
7. Direct hits.
8. Inability to withdraw from a gassed area.
9. Enforced advance through or occupation of a contaminated area.
10. Lack of gas defense materials.
11. Unprotected quarters.
12. Disobedience of gas orders.
13. Wearing contaminated clothing after attacks; inability to wash the surface of the body.
14. Food and water contamination.
15. Use of contaminated firewood, both from contact and from the vapor thrown off during the burning of the wood.
16. Handling of contaminated clothing.
17. Sleeping in contaminated dugouts, using infected blankets.
18. Seeking protection in supposed gasproof dugouts.
19. Exhaustion and resting on contaminated soil, or in contaminated woods.
20. Lack of warning—when sleeping.
21. Remaining in the path of shifting winds coming across gassed territory.
22. Failure to heed the effects of long stay in a vapor exposure of low concentration.

ACTION AND TREATMENT OF LUNG IRRITANTS

Inhalation of these gases in strong concentrations induce, some hours after their entrance into the system, an intense edema of the lungs with considerable outpouring of fluid into the lung tissue.

The three principal gases coming under this head are: Chlorin, phosgene and chlorpicrin.

In discussing the clinical aspects of lung irritants, it must always be remembered that there are several things to be considered and that no hasty conclusions must be drawn. The action of these gases on the human being is the same whether they are liberated from shells during bombardments or from cylinders in cloud attacks. The severity of the symptoms resulting from them depends upon the degree of concentration of the gas, the amounts inhaled, the power of resistance of the individuals exposed, their behavior during and after the gas attacks, and the use of artificial protection such as gas masks, protective suits, etc.

The delayed action of gases is also an important factor which must be given great weight. At times this phenomenon is most pronounced and often it cannot be explained. The writer recalls very distinctly being present at a gas attack which took place on the Western Front, during which several hundred casualties occurred. The majority of those affected presented the symptoms usually expected in cases of this kind. However, in a large number, the symptoms did not become apparent until after the expiration of six hours. This was a typical example demonstrating the phenomena of delayed symptoms. All of the participants in this bombardment were exposed to the same concentrations of gas and under the same conditions, but for some unexplained reason there was a marked delay in some in the appearance of gas effects.

The British report the following striking example of this delayed effect:

> "A patient was observed from start to finish after only a brief exposure to a strong concentration of phosgene. The greatest care was taken to prevent any muscular exertion so that no complicating factor was introduced. The immediate irritant symptoms and coughing that were produced during the exposure soon diminished in fresh air, and an hour and a half later there was no coughing and the patient seemed particularly well, the pulse being normal. The condition remained quite good until four and a half hours after exposure to the gas when the patient got bluish about the lips. Coughing then recommenced with expectoration of frothy sputum. Soon the lips and face became of a gray ashen color though the pulse remained fairly strong. About four pints of clear frothy yellowish liquid were coughed up from the lungs in the next hour and a quarter, and at the end of this time the patient expired. At no time was there any great struggle for breath nor did the patient realize at all how bad he was."

After our entry into the War, much difficulty was experienced in our field hospitals and advance relief stations in preventing gas patients with delayed symptoms from moving about. The error was commonly made in permitting them to walk back to latrines three or four hundred yards away, or to move about in the wards. As a result, many of these men developed sudden progressive dyspnea followed by cyanosis and death.

Classification of Cases.—In the usual course of events, irritant gas cases may be divided into the following:

Suspicious cases, or those presenting few symptoms.

Mild cases, or those suffering severe headache, dizziness, burning sensation in the throat, accompanied by slight coughing, nausea, and perhaps vomiting.

Medium severe cases, or those presenting the above symptoms, but to an exaggerated degree.

Severe cases, or those with marked cyanosis, evidences of pulmonary edema, and failing circulation.

No conclusions can be drawn from the general appearances of early gas cases for the reason that the action of a concentrated gas for a short period may cause a most intense corrosive effect while at the same time but a small amount of the poison has been absorbed in the blood. On the other hand, the inhaling of a diluted gas for long periods and without apparently any corrosive action may produce far greater toxic effects.

These gases affect:

1. The skin.
2. The eyes.
3. The mucous membranes of the respiratory passages.
4. The circulatory organs and the blood.
5. The respiratory mechanism.
6. The organs of digestion and the urinary organs.

The effect on the skin is usually mild. They may produce slight redness and some swelling and, although not considered as lacrimators, they cause burning of the eyes and secretion of tears, with slight injection of the conjunctival vessels and in many cases superficial erosion of the cornea. Their main action, however, is exhibited in the organs of respiration.

As a rule the first place in which the action of gases of this kind becomes apparent is in the deeper air passages and the alveoli of the lungs. Here an inflammatory action takes place, which is generally characterized by a mild congestion, swelling of the mucous membrane, increased secretions into the air tubes, and a marked edema formation with an inflammatory exudation in the lung tissue. The main clinical features may be summarized as follows:

1. Attacks of coughing, catching of the breath.
2. Inability to expand the chest.
3. Nausea, vomiting, nosebleed and shallow respiration.
4. Cyanosis.
5. Feeling of pressure across the chest, followed by breathlessness which may be absent or not become apparent until after the lapse of four or five hours, depending upon the concentration of the gas and the duration of exposure. In the lighter cases the symptoms, which generally disappear during the first forty-eight hours, may be restricted to headache, nausea, giddiness, and a burning sensation in the throat.

Men exposed to strong concentrations of phosgene and who fail to apply their masks immediately may die in a few hours from acute pulmonary edema or in some cases from a cessation of the pulmonary reflexes. Their distress in the interval becomes intolerable, they wail and groan, struggle for air, grasping at their throats, tearing open their neck coverings, and tossing themselves restlessly about with a view of obtaining more air. The color of their faces varies from a bluish red to deep cyanosis.

Their breathing is irregular, faltering, and very shallow. They bring into play all of their auxiliary muscles of respiration. They hack and cough, expectorating a large amount of blood-streaked sputum, resembling greatly that of pneumonia. The stethoscope reveals many widespread crackling râles with areas of diminished breath sounds.

A pulmonary edema of this kind may cause death in a few hours, or during the course of the first or second day. On the other hand, the case may pass on to a condition greatly resembling a diffuse bronchitis, with glassy, slightly blood-stained, rusty or lemon-colored sputum, followed in the course of thirty-six hours by a mucopurulent expectoration. In the majority of cases of this type, the body temperature is increased from 38° to 40° C.

The cases presenting symptoms of pulmonary changes in the beginning are not as a rule the only ones to contract bronchopneumonia. Ofttimes the pulmonary symptoms may be entirely absent on the first or second day when suddenly, at the end of from forty-eight to seventy-two hours, fever may set in with all the symptoms of bronchopneumonia. As a rule the history of these cases shows that they had been exposed for long periods to gases of a low concentration, or that the early symptoms had been overlooked. In the majority of cases, the bronchopneumonia which develops during the first or second day, and which seems to be due directly to the action of bacterial infection, does not prove fatal. The symptoms generally disappear with a marked fall in the body temperature during the second or third day.

The early bronchopneumonia, when it occurs, is generally distinguished from the acute pneumonia of the later stages by the fact that in the latter the symptoms may not appear for several days. The onset is usually marked by high persistent fever, and the disease confined to the lower lobes. The characteristic symptoms are widespread areas of dulness over the lower chest, bronchial breathing, loud râles, rusty sputum, and evidences of pleurisy which may be either dry or accompanied by affusion. This condition is evidently due to a subsequent bacterial infection, favored by the action of the gases on the lung tissue, and its course resembles that of ordinary inflammation of the lungs. It is responsible to a large degree for the deaths which may occur during the second or third week.

In the majority of cases, and even in those exhibiting severe symptoms of pulmonary edema and bronchopneumonia, convalescence is fairly rapid and the pulmonary symptoms disappear, leaving no after effects. In some cases, however, the symptoms do not disappear entirely and pulmonary trouble may persist for weeks, sometimes with alternating periods of improvement and retrogression. In a few cases, the existing diseases of the lungs, such as tuberculosis, may be accentuated under the influence of gas poisoning, but cases of this nature are very rare.

Definite objective changes in the upper respiratory passages are found in exceptional cases due to the intense action of a concentrated gas mixture. Such changes comprise redness and swelling of the mucous membranes, with the occasional formation of a grayish-white membrane or even slight ulceration of the throat and larynx. Patients frequently complain of burning and dryness of the throat, hoarseness occurring in a small number of cases. It is not improbable, however, that the intensive action of a concentrated irritant gas coming in contact with the upper respiratory passages may cause spasms of the laryngeal and respiratory muscles, thereby resulting in death from asphyxia.

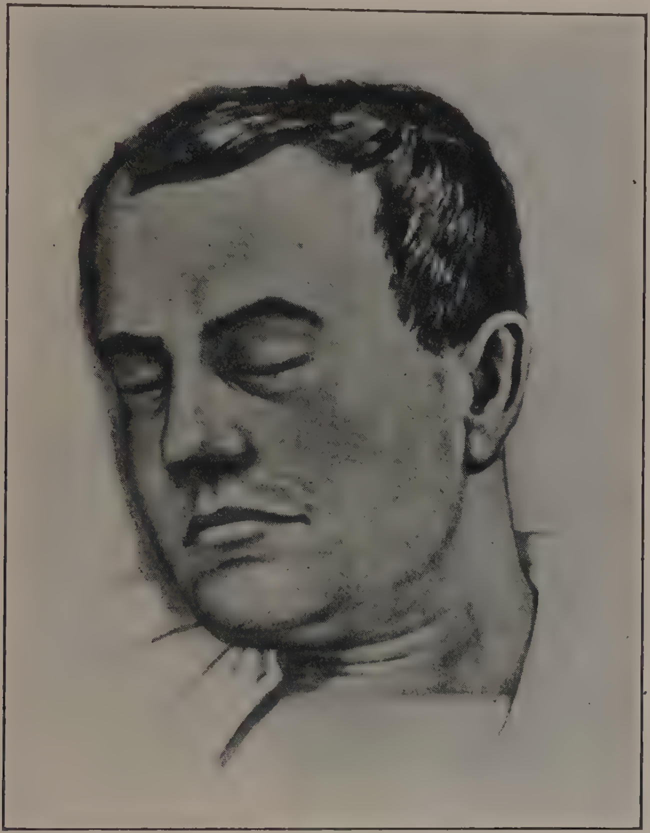

Fig. 3.—Blue Type of Asphyxia from Phosgene Poisoning Showing Intense Venous Congestion. Drawing made thirty hours after exposure to the gas. Illustration from *Atlas of Gas Poisoning* provided for the American Expeditionary Force by the American Red Cross, 1918.

As a rule, the first place in which the violent action of the gas becomes evident is in the deeper air passages, and in the alveoli of the lung. This irritation is immediately followed by an inflammatory reaction, characterized by congestion, swelling of the mucous membrane, increased secretion in the air tubes, edema formation and inflammatory exudation into the tissues of the lungs.

The cases in which pulmonary edema develops to a serious extent resolve themselves into two groups. *The first group*—blue type of asphyxia (see Fig. 3)—comprises cases which show definite venous engorgement; the face is congested and deeply cyanosed; the lips and tongue are a full blue color; and there may be visible distention of the superficial veins of the face, neck or chest. There is usually considerable degree of true hyperpnea, that is, the breathing is not only increased in frequency, but the actual amount of air reaching the lungs per minute is markedly above normal. Cough may be present, and expectoration of large quantities of a thin frothy fluid is more likely to occur in this group than in the other. The pulse rate is usually a little over 100 per minute and is full and of good tension.

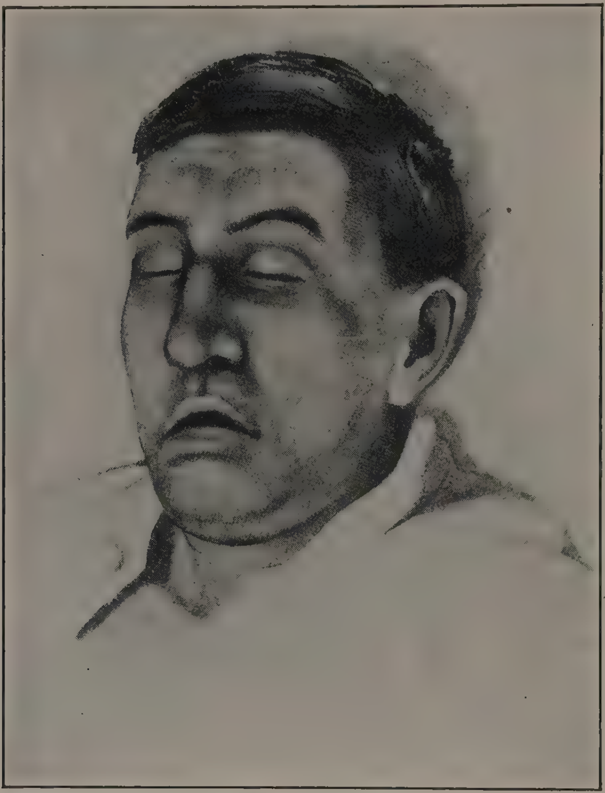

FIG. 4.—GRAY ASHEN TYPE OF ASPHYXIA FROM PHOSGENE POISONING WITH CIRCULATORY FAILURE. Drawing made on second day after gassing. Illustration from *Atlas of Gas Poisoning* provided for the American Expeditionary Forces by the American Red Cross, 1918.

In *the second group*—the gray type of asphyxia (see Fig. 4)—cases show an ashen pallor rather than deep cyanosis, the lips being pale and leaden colored, and the patients are in a general state of collapse. Respiration is rapid, but the increase in rate is partly compensated for by the shallow character of the breathing so that the actual hyperpnea is slight. Though the lungs are intensely edematous, there is often little expectoration, and cough is infrequent. The pulse is very rapid (130 to 140 per minute), weak and running. The prognosis is much worse than in the first group. Cases of the second group predominate in phosgene poisoning, but many intermediate types are seen. Sometimes a case which at an earlier stage has shown congestive cyanosis with a full pulse may gradually assume a gray pallor with an accelerated and weakened pulse.

Blood.—There is no immediate destruction of the blood or the formation of poisonous products as a result of lung irritants. The hemoglobin is not changed, and its oxygen capacity remains the same. The carbonic acid content of the arterial and venous blood is not lowered, but, on the contrary, is slightly raised. There is marked concentration of the blood and an alteration in the blood gases, which is caused by the loss of the plasma of the blood as it passes into the lungs and, to a certain extent, by the viscosity or internal friction of the blood and the increased amount of carbonic acid.

At the height of illness, more than half of the blood plasma may leave the circulatory system and pass into the lungs, and the number of red cells becomes increased to the extent of 8,000,000 or 9,000,000 to 1 c.mm., while the hemoglobin content will also be greatly raised. As a rule, in from six to eight days these conditions improve and the pulmonary edema becomes reabsorbed.

During the first few hours after gassing, the coagulation rate of the blood is increased. The gassed blood, in fact, greatly resembles the blood after asphyxiation; that is, there is less oxygen and more carbonic acid, the degree of cyanosis being an index of the diminution of the oxygen content. There is also a great difference between the arterial and the venous blood in the oxygen content. Thrombosis may occur at any time, due to the retarding of the circulation, probably caused by the viscosity.

Circulation.—The disturbance of the circulation depends to a great extent on the amount of poison in the system. In mild cases and in the early stages of severe gas poisoning, the pulse rate is usually regular and strong, but somewhat slow. At the height of the illness, however, the activity of the heart is greatly impaired by the following conditions: want of oxygen, excess of carbonic acid, interference with the circulation (mainly due to the resistance in the lungs at the height of edema), impairment of nutrition of the heart from diminished circulation, increased viscosity and increased exertion of all the respiratory muscles.

In the more severe cases of gas poisoning the pulse rate may be increased to 160 or 170 per minute, at the same time becoming small, soft and at times scarcely palpable. These conditions are generally met with in the ashen gray cases. Although the lungs are greatly distended, it is generally possible to percuss the outline of the heart and hear the cardiac sounds. The blood-pressure may remain normal, but as a rule it becomes lowered with the appearance of pulmonary edema. This condition may remain for a week or ten days.

The cause of this drop in blood-pressure is not fully known, but it is not believed to be due to the excitation of the vagus. In the marked cyanotic cases the blood-pressure is slightly raised, which is believed to be due to the asphyxial excitation of the vasomotor center. As a rule the failure of the heart is usually gradual, but it may develop suddenly. Such factors as advanced age, previous heart disease, overexertion, lack of rest and irregularity of habits induce circulatory disturbances. In some cases marked puffiness of the face, hands and feet have been observed at the height of the illness. Slight hemorrhages in the skin, the endocardium and pericardium, the brain and the mucous membranes of the alimentary canal are often noticed.

Nervous Mechanism.—The disturbance of the nervous mechanism of the body following gas poisoning generally becomes apparent at the very beginning and is usually indicated by a severe frontal headache which as a rule disappears during the first twenty-four hours after exposure. Associated with this are giddiness, staggering gait, muscular weakness, diminution of tendon reflexes and a general dulling of sensibility. This combination of symptoms is not always present, especially in those cases showing marked pulmonary edema. On the other hand, cases exposed to the gases for some time at low concentrations, and which presented few symptoms of irritation of the respiratory passages, suddenly developed exaggerated nervous conditions but generally of a transitory nature. With prolonged respiratory insufficiency and deep cyanosis, dulling of sensibility developed due to "asphyxia auto-intoxication," or deficiency of oxygen and excess of carbon dioxid.

Psychical disturbances of a more or less severe character, either transitory or the reverse, occur in a large number of cases. Confusion, stupor, failure of memory, disturbances of speech, delirium, mental disturbances, and even maniacal conditions might be present. As a rule these nervous phenomena disappear without leaving serious sequelæ.

Digestive Disorders.—Vomiting is very common in connection with all gassed cases, but as a rule rarely persists longer than a day. Gassed cases generally complain of loss of appetite, pain in the stomach, malaise and nausea. In some of the cases, the symptoms resemble those resulting from a central toxemia. Some cases complain frequently of a more or less severe pain in the region of the stomach and lower bowels which may continue long after complete recovery from the gas poisoning and which does not respond to treatment. Diarrhea, with occasional blood in the stool, may be encountered but it is of small consequence.

Urinary Organs.—In the majority of cases, the urinary organs are not affected. However, difficulty of urination, or retention of urine, may occur in occasional cases, but these conditions can generally be attributed to nervous influences. The quantity of urine is not materially altered except when there are severe disturbances of circulation. Albuminuria is occasionally present during the first twenty-four hours, but it is generally of a transitory nature.

During one of the engagements on the Western Front, the writer recalls an incident in which 410 soldiers were gassed severely. Of this number 200 were removed to a hospital at some distance behind the line; the remainder were hospitalized nearby. All of the former cases presented marked symptoms of albuminuria but of a transitory nature, while in the latter 210 cases no albumin was found. This condition was accounted for by the fact that the 200 cases in which albuminuria was present had been on the train for more than twenty-six hours, during which time they suffered many privations, while the latter cases were hospitalized in less than two hours.

During the reabsorption of the edema from the lungs, there is generally an increased amount of urine.

Deaths.—Most of the deaths from lung irritants occur during the first twenty-four hours with symptoms of pulmonary edema and failure of the circulation. Deaths occurring on the second or third day are generally due to inflammatory conditions of the lungs. Gas cases surviving until the third day without serious symptoms generally recover, but, on the other hand, a case is not entirely free from the possibility of the development of latent grave symptoms before the end of the first week.

Prognosis

A prognosis can only be made with the greatest caution during the first few hours. The majority of the cases can be grouped, almost from the beginning, into classes—mild or moderately severe. As a rule the quite trivial cases and the quite hopeless ones may be quickly recognized. On the other hand, it must not be forgotten that apparently slight cases may suddenly develop very severe symptoms, while other cases having most alarming symptoms may, after the lapse of a few hours, show a decided improvement.

General Treatment of Lung Irritants

In view of the multiplicity of symptoms, together with their varying degrees of severity, it is almost impossible to render a definite line of treatment for these cases. As a result, the individual peculiarities of each case must be studied separately and the form of treatment prescribed accordingly. The delayed action manifested in many of these cases is also a factor which must be given much weight.

In the general treatment of all gas cases there are, however, a few fundamental rules applicable to all, which should be followed; (1) remove all patients or suspects from the reach of poisonous gases as quickly as possible; (2) consider every person exposed to the fumes of poisonous gases and who may or may not present any symptoms thereof as gas casualties and treat them as such until proved otherwise.

In outlining a treatment for these cases, the fact must always be borne in mind that the grave issue to be met is pulmonary edema, and that the conditions to be overcome in connection with it are oxygen want, condensation of the blood, and overloading of the right heart.

With an understanding, therefore, of these conditions, the principles to be inculcated in overcoming them may be summed up as follows:

1. Absolute rest for the purpose of restoring respiratory activity.
2. Body warmth.
3. The administration of oxygen.
4. Venesection.
5. Improvement of the circulation.
6. The endeavor to rid the body of accumulated poisonous gas products.
7. The prevention of the oncome of secondary infections.
8. The alleviation of pain.
9. Intravenous injections of Gum Arabic and Glucose.[1]

Absolute Rest.—Too much emphasis cannot be laid on the importance of rest, and the greatest care must always be exercised to prevent muscular activity. Patients should not be permitted to walk, either alone or with assistance, but on all occasions should be carried by stretchers or other means whenever possible. In the very severe cases, it may be hazardous to the patients to move them even by this means and, unless conditions so demand, they should not be disturbed. It must be remembered that all muscular work is done at the expense of increased activity of the heart, which may frequently lead to fatal termination.

Body Warmth.—Cold has much the same effect on gas cases as exercise in producing oxygen want and pulmonary edema. Therefore, warmth ranks second in importance to rest. It may also be necessary to combat shock from exposure and want.

The Improvement of the Oxygen Supply.—The early administration of oxygen is of vital importance to all cases, especially those showing evidences of cyanosis. It must be remembered that the gray ashen cases are just as definitely suffering from oxygen want as those showing evidences of cyanosis. The comfortable support of the body in a position that renders the breathing as easy as possible is also of great importance, and as a rule the feelings of the patient must be taken as a guide. Gas cases assume different attitudes when in bed. Some prefer to lie flat on their backs, in which position breathing with little muscular effort is more readily possible, while, if the body is raised, a deep type of breathing with much muscular effort would result. Other cases prefer to lie on the side with limbs drawn up. As a rule these cases remain absolutely quiet and motionless, because movements of any kind bring on spasmodic attacks of coughing.

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[1] Vedder and Sawyer of the Medical Corps of the Army recently found, in their experiments conducted at the Research Laboratories at Edgewood Arsenal, that the lives of dogs severely gassed with pulmonary irritants could be saved, if within a few hours after exposure to the gas they were given intravenous injections of a solution containing gum arabic 25% and glucose 25%. For ordinary sized dogs from 200 to 225 c.c. of the solution was used.

The best method for giving the oxygen treatment is by inhalation. The injection of oxygen or introduction of oxygen by the venous route is worthless. The amount of oxygen to be administered depends upon the severity of the case. It should be administered as continuously as possible during the entire period of the illness, the object being to tide the patients over the critical stage during the first few days. The administration of oxygen with an apparatus fitted with face-piece and reducing valve is essential for the reason that the supply can be regulated. There are several standard makes adopted for the purpose; all are good but none are as satisfactory as an oxygen chamber in which the patient can be placed.

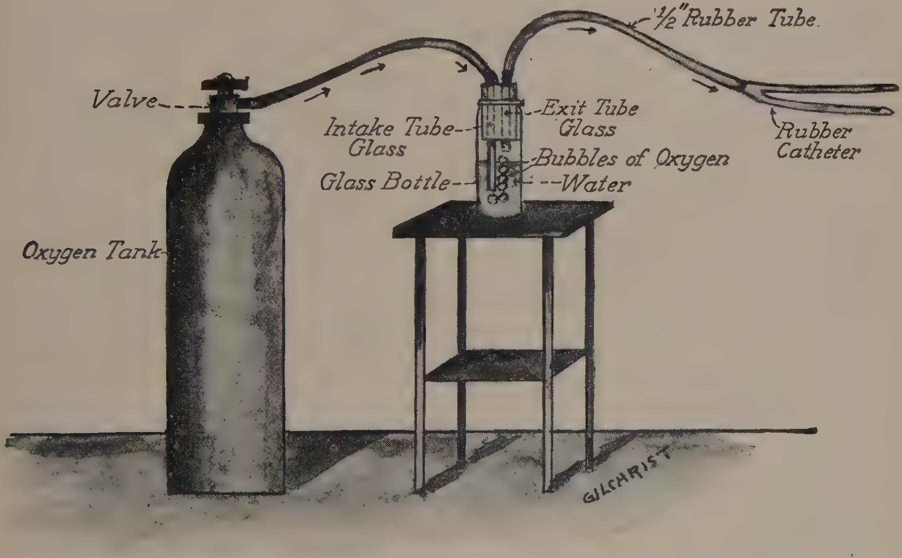

FIG. 5.—SIMPLE PRACTICAL METHOD OF ADMINISTERING OXYGEN.

Emergency Apparatus for the Administration of Oxygen.—If it is impossible to obtain one of the standard makes of oxygen masks, the following improvised emergency apparatus can be readily prepared. (See Fig. No. 5.) This apparatus was used very successfully during the War both by the British and our own troops. It is simple of construction, safe and reliable.

The materials necessary for its construction consist of the following:

1 glass bottle, 1 to 2,000 liter capacity, wide mouth.

2 pieces of ¼ glass tubing, lengths 10 inches and 3 inches.

2 soft rubber catheters.

2 pieces of ½ inch rubber tubing of lengths sufficient to connect the intake tube of the glass bottle with the oxygen tank, the other to connect the outlet tube of bottle with the soft rubber catheters passed into the posterior nares of the patient at rest.

Description of Apparatus.—The cork of the bottle is perforated with two holes, ¼ inch in diameter for the reception of the intake and outlet glass tubes. One end of the ½-inch rubber tubing is attached to the projecting end of the glass tube through the cork, the other to the valve on the oxygen tank.

The other rubber tubing is attached to the projecting end of the small glass tube and the other end is secured to the soft rubber catheters.

If it is impossible to use the double catheters in the nares a single one may be used to good advantage.

By passing the oxygen through the water in the bottle, the supply can be regulated by the number of bubbles produced.

When using the soft rubber catheters they are passed into the posterior nares and secured in position by adhesive tapes.

In using the mask the oxygen must never be turned on suddenly for fear of startling the patient and the flow must be commenced before the mask is applied. As a rule, 6 liters per minute is sufficient for the average gas case. In administering the oxygen great care must be exercised at all times to prevent the flow under too great a pressure for the reason that rupture of the lungs, interstitial, emphysema, or even subcutaneous emphysema may result. (This is questionable.)

Oxygen to be of value must be maintained as long as cyanosis is present. In serious cases with marked cyanosis difficulty of breathing and unconsciousness, it may be necessary to resort to artificial respiration.

Venesection.—The alteration of the air passages owing to the swelling of the mucous membrane in the finest bronchioles, together with the flooding of the alveoli with edematous blood and inflammatory substances, may not only hinder the entrance of air during respiration, but may even render impossible the entrance of oxygen to the pulmonary capillaries. In such cases venesection should be performed early and at the appearance of the first signs of pulmonary edema. To be efficacious, from 300 to 500 c.c. of blood must be removed, and this process can be repeated after five hours or oftener if necessary. By the removal of the blood it not only diminishes the viscosity, but at the same time relieves the edema of the lungs, thereby causing a general improvement in the condition of the circulation.

It is often impossible to obtain the required quantity of blood from the veins at the height of the disease, and for this reason it is of the greatest importance to perform venesection early and before the blood becomes too thick. A good method of performing venesection is by making a simple incision into a vein in the arm and allowing the blood to flow out. Massage of the forearm and active movements of the hand will greatly increase the flow. Should the blood refuse to run, the injection of a salt solution into the vein will assist it.

Treatment During the Convalescent Period

Early recoveries are made in the general run of gas cases. Patients developing secondary infections and those showing cardiac symptoms offer problems which at times are most trying to the physicians. These patients must be watched carefully, especially those apparently normal, but who physical exercise develop severe attacks of dyspnea.

In order to differentiate gas cases, each one should be started on graduated exercise as soon as possible, and the result of this exercise should be a guide as to the general condition. After a patient has been up for three or four days, a moderate walk of a few hundred yards should be undertaken and, if no signs of breathlessness or increased pulse rate are noted, a longer walk should be repeated on the following day, which should be gradually increased each succeeding day. If after the increased exercise there are evidences of shortness of breath or tachycardia, all exercise should stop for a few days, keeping the patient quiet after which the graduated exercise should again be commenced.

The best treatment for breathlessness and increased heart action, and in fact for any of the after effects of gassing, is the general routine of administering small amounts of oxygen. Certain drugs have also been recommended for these conditions. Thayer, Douglas and others recommend camphor or caffein to be administered hypodermically, and in the severe cases a little digitalis, especially in those showing cardiac complications. All agree, however, that it is inadvisable to use atropin and adrenalin for the reason that they cause an increased strain on the heart.

ACTION AND TREATMENT OF VESICANTS

These substances are distinguished from the lung irritants by the persistence and insidiousness of their action. The two principal gases coming under this head are dichlordiethylsulphid, or yperite, commonly known as mustard gas, and chlorid of diphenylarsin or arsin, the first being liberated in minute drops, the second in extremely small solid particles which are invisible. Dichlordiethylsulphid, or mustard gas, is the best vesicant known, although not to be considered in the same category as phosgene, chlorin, diphosgene, chlorpicrin and gases of similar characteristics so far as lethal effect is concerned.

These gases are powerful vesicants. They have but little smell which is noticed immediately after the shell burst and suggests the odor of mustard for the former, or garlic for the latter. The exact mechanism covering their effect on the human body is not fully understood. There are several theories regarding this phenomena, but as yet none has been satisfactorily explained. The most plausible one, however, is that the action is due to the liberation of hydrochloric acid in the cells from hydrolysis, thereby causing a breaking up of the compound into hydrochloric acid and another body.

These vesicants have many features which commend them for a weapon of this sort. They are toxic in concentrations and penetrate all clothing, affect the skin and mucous membranes. They are painless in action on the skin so therefore cannot be detected in this way. Death is not the direct result of the action of the liquid or the poisonous vapor, and when it occurs following exposure it is generally the result of secondary bacterial infections. The clinical manifestations and the severity of the symptoms produced depend upon the degree of exposure, and the casualties produced by it may be divided into mild or light cases and severe or serious cases.

In the light cases, the first symptoms generally encountered are headache, swelling of the eyes, accompanied by photophobia, later a feeling of dryness in the mouth, throat, accompanied by slight cough and vomiting; areas of redness accompanied by irritation and itching of the skin over unprotected parts, especially the face and neck. These cases generally clear up in from twenty-four to forty-eight hours, although a stubborn cough and hoarseness may remain several days following.

The main features of severe mustard gas cases may be summed up as follows:

1. Delay in the effects of the gas from three to four hours.
2. Nausea, vomiting, burning sensation in the eyes, dryness of the mouth, throat, and hoarse dry cough accompanied by pains across the chest.
3. Intense conjunctivitis, generally accompanied by complete closing of the eyelids rendering temporary blindness.
4. Marked areas of redness on the exposed and moist surfaces of the skin, especially the face, neck, axillæ and groins, followed by blister excoriations and brown staining.
5. Inflammatory necrosis of the mucous membrane of the trachea and bronchi, with infective bronchitis or septic bronchopneumonia.

The actions of vesicant gases are always delayed; even high concentrations produce no immediate irritation of the superficial sensory nerves. The first symptoms observed are redness of the skin accompanied by burning and itching sensation, severe frontal headache, malaise and nausea, vomiting and burning of the eyes. In exceptional cases, however, these symptoms may show up during the first hour or two. Their main action is on the skin, the eyes, mucous membranes of the upper respiratory passages, and the lungs. They may also be absorbed, causing functional disturbances of the circulatory system, nervous system, and alimentary canal. The degree of symptoms produced depend upon whether the person was exposed to the liquid itself or to the vapors, the liquid producing by far the greater amount of damage. (See Fig. 6.) The effect on the skin depends to a large extent on the individual sensitiveness of the person exposed and the part of the body affected, delicate-skinned persons being more readily affected than those with coarser skin.

Approximately 50 days after application, healing is nearly completed, the lesion consisting of a thin scar, pinkish white in the central portion and whiter, more opaque, at the periphery, with very slight puckering. Around this is a brown pigmented areola. The whole area, however, is redder than normal skin (see Fig. 7).

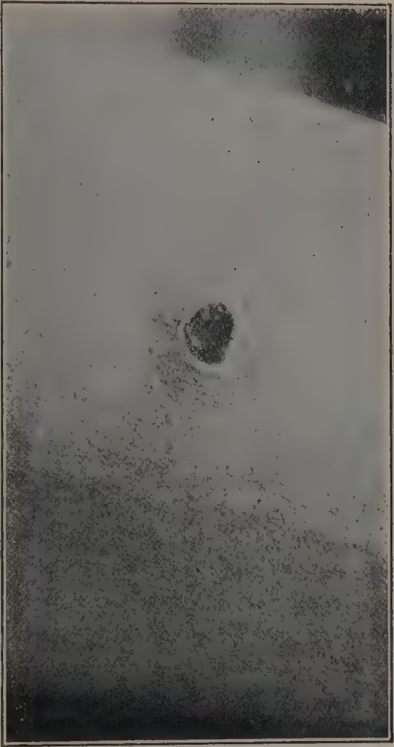

FIG. 6.—MUSTARD GAS LESION. This is shown nine days after application. Beginning separation of necrotic base from peripheral white zone.

Effect on the Eyes.—In all stages of poisoning by mustard gas, the eyes are affected, the degree of affection depending on the concentration of the gas and the length of exposure. In from three to four hours after exposure to a vesicant gas, the eyes become red and feel as if a foreign body had entered. They burn severely, and this is followed by an increased secretion of tears. The conjunctival vessels become injected, which condition generally increases until a typical appearance is presented at the end of twenty-four hours. The lids are swollen and the patient is virtually blinded, with tears oozing between the bulging eyelids. Photophobia is well marked. A copious purulent secretion collects in the corners of the eyes which may pass into a purulent form. At times it is impossible to open the eyes.

The violent inflammation may extend to the internal part of the eye, affecting the iris and ciliary bodies which become hyperemic. In these cases a well-marked catarrhal condition is present, with swelling of the mucous membranes and increased secretions. The cornea is hazy, the patient claiming that his sight is obstructed by a thin veil. After four to five days these symptoms gradually subside. The pupil clears up, and signs of conjunctivitis disappear and, at the end of two or three weeks, barring complications, the average case has entirely recovered.

As a rule there are no after effects following these eye symptoms, a good recovery being the usual phenomena. In severe cases, due to cicatrization, there may be impairment of vision or even loss of sight. As a rule the eyes are sensitive to light and dust for some time after recovery.

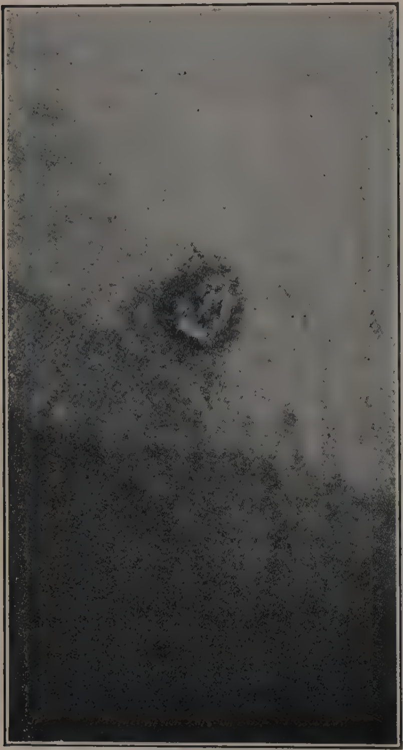

FIG. 7.—MUSTARD GAS LESION. This is shown forty-nine days after application. Scar with brown pigmented areola. Slight puckering of scar.

Action on the Respiratory Tract.—The effect of mustard gas is always pronounced on the respiratory tract, especially the upper passages. Like the suffocant gases, the concentration of the gas, length of exposure, protective appliances used, etc., regulate the degree of severity.

These cases may vary from mild to severe. In the mild cases the mucous membrane shows but slight inflammation which may involve the surface of the pharynx and the larynx. In the more severe cases the redness and swelling are increased, which with the increased secretion of mucous membrane of the nose, larynx and throat render a condition quite similar to a severe coryza.

As the disease progresses, the redness and swelling of the nose increases, accompanied by a mucopurulent discharge. These phenomena are accompanied by soreness and the formation of crusts in the nostrils. The tonsils become enlarged and angry looking; swallowing is extremely difficult. The mucous membrane of the larynx and pharynx becomes edematous and covered with a mucous secretion. The vocal cords, especially the false ones, show similar changes.

Laryngitis is always present, and as a rule the voice is husky, the patients at times being unable to utter a sound above a whisper. Coughing, accompanied by retching, is a common phenomenon, while the symptoms of bronchitis may be apparent, it is the exception rather than the rule to find conditions of this kind resulting from this cause.

The sputum is mucopurulent and the body temperature may be raised from two to four degrees. In the very severe cases, the inflammatory conditions are well marked in the upper air passages, and may bring about serious changes in the mucous membrane and the parts affected. These exudations may become solidly organized due to the excretion of fibrin and cellular elements. The upper layers of the mucous membrane become necrotic with the resultant formations of false membranes especially in the throat, and may produce a condition greatly resembling a case of diphtheria of the larynx.

The element of bacterial infection must always be apprehended, and with its presence the formation of necrotic and ulcerative areas of mucous membranes may take place in the throat and result seriously. In the severe cases the suffering is untold. The patients remain listless and experience the greatest difficulty in swallowing, and occasionally asphyxia resulting from closing of the glottis may take place. In these cases, bronchial pneumonia may develop with all of the clinical manifestations, the disease may finally pass into a rapid and fatal termination presenting many of the characteristics of a pulmonary edema, due to the inhalation of suffocant gases.

The effects of vesicant gases are usually severe in the crotch; the swelling of the prepuce, the copious secretion in the preputial sac and the ulceration of the mucous membrane greatly resemble conditions produced by venereal diseases. Permanent scars are generally left or can generally be found over areas which have been burned by vesicant gases. These scars may be slightly depressed or may be simply outlined by colored pigment. In many cases, mustard gas produces an erythematous condition of the body which greatly resembles nettle-rash. This is generally found on persons who perspire profusely. Rare instances have also been reported in which a weeping eczema resulted from exposure. Attention is invited to the chart on page 760 which was prepared from records made by the writer in examining over 3,000 men of all arms of the service suffering from the effects of mustard gas seen during his service in France. (Fig. 8.)

A casual analysis of the chart reveals some very interesting information. It will be observed that the part of the human body, that is, the face, which is provided with the best protective apparatus furnished the greatest percentage of wounds. Of the 3,000 cases examined, 2,538, or 85 per cent, had eye affections, and 2,340, or 78 per cent, suffered from throat involvement. All of these men were provided with box respirators or gas masks, which, if properly worn, should have furnished absolute protection against these gases. The large percentage of wounds on parts of the body supposed to have been protected against them revealed one of two things: either the masks were defective or that the men did not use them properly.

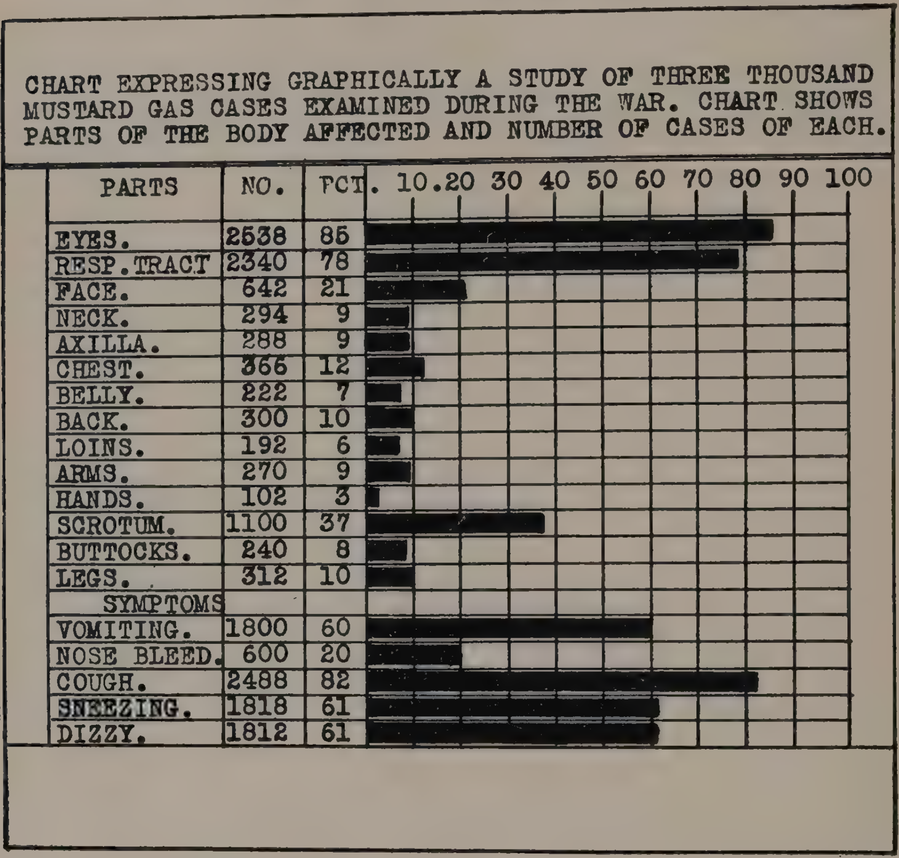

CHART EXPRESSING GRAPHICALLY A STUDY OF THREE THOUSAND MUSTARD GAS CASES EXAMINED DURING THE WAR. CHART SHOWS PARTS OF THE BODY AFFECTED AND NUMBER OF CASES OF EACH.

PARTS	NO.	PCT.
EYES.	2538	85
RESP.TRACT	2340	78
FACE.	642	21
NECK.	294	9
AXILLA.	288	9
CHEST.	366	12
BELLY.	222	7
BACK.	300	10
LOINS.	192	6
ARMS.	270	9
HANDS.	102	3
SCROTUM.	1100	37
BUTTOCKS.	240	8
LEGS.	312	10
SYMPTOMS		
VOMITING.	1800	60
NOSE BLEED.	600	20
COUGH.	2488	82
SNEEZING.	1818	61
DIZZY.	1812	61

Fig. 8.—Graphic Chart Taken from the Official Report of Colonel Gilchrist, Chief of the Medical Division, Chemical Warfare Service, U. S. A., 1922.

With every reason to believe that the masks were not defective, it means that the cause was due to their improper use or lack of training. The chart also shows that the most exposed parts, that is, the hands, were scarcely affected by the gas. This can only be explained by the thickness of the epidermis which offered a natural protection, for, as shown by the large percentage of scrotal affections, which undoubtedly were caused by contact from the hands when attending to nature's wants, the hands must have been contaminated with the gas.

PROPHYLAXIS

During the War a variety of methods were used by medical officers of the army in the treatment of conditions produced by exposure to mustard gas. Some of these methods of treatment were good; others bad. One reason for this apparent lack of uniformity concerning a matter of such great importance was due to the fact that, prior to the introduction of mustard gas by the Germans on the Western Front, little was known concerning this weapon or its effects.

Shortly after its introduction, however, medical officers of the Allied armies began immediate research and before long much valuable information was at hand. This research work was conducted not only in the hospitals and laboratories in France, but also in the United States by some of the leading medical men.

The treatment of mustard gas cases is so closely interwoven with that of prophylaxis that before beginning this subject a few words will be devoted to the latter, mentioning particularly methods of ridding areas, clothing, etc., of the poison from mustard gas. In view of the clinging properties of this gas, ground and surroundings contaminated by it are dangerous to those coming in contact with it for days or weeks following. If the areas are to be occupied or are in close proximity to habitations, they should be cleaned up or degassed.

The best way of accomplishing this is with bleaching powder which neutralizes the mustard gas, changing it to the harmless tetrachlorethylsulphid. When using bleaching powder for this purpose, it must be dry, the wet powder being very unreliable. It should be spread very slowly and the entire surfaces covered. If rapidly done, the powder will drive off the mustard vapor faster than neutralization can take place.

It is very important to be able to detect the odors of mustard gas, and the best time of the day for this examination is during the early morning hours when the mist is rising.

Degassing of Clothing and Materials.—The freeing of garments and materials contaminated with mustard gas requires much care and precaution on the part of those engaged in the work to avoid becoming infected, and gas masks, rubber gloves and protective suits should always be worn by those exposed. There are two general methods of removing the poisonous fumes of these gases—chemical and physical.

Chemical Methods

Chlorid of lime.
Chlorin.
Oxidizing agents—potassium permanganate.

Condensation with anilin.
Alkaline soap wash.
Use of sodium bicarbonate wash.

Physical Methods

Heat.
Neutral solvents—running cold water.
Steam under pressure.
Steam not under pressure.
Sunlight.
Open air.

The best methods for degassing clothing are with the steam sterilizer, or steam under pressure; and the Serbian barrel and steam box, in which steam is used not under pressure. These methods, although not entirely satisfactory, are rapid. With the steam sterilizer, the contaminated clothing should be treated with live steam for twenty minutes, following which it should be exposed to hot air for ten minutes. With the Serbian barrel, or steam box, one hour is required for accomplishing this purpose. The use of hot water and alkaline soap requires from six to eight hours; cold running water, two days, and exposure to sunlight one week.

Bathing as a preventive was used extensively during the War. For this purpose the Gilchrist mobile bathing plant was extensively used. With this plant, 700 men could be bathed and degassed in one hour. This plant consisted of a large, motorized tank car carrying 1,200 gallons of water with heating and pumping devices together with 24 showers and clothing for 500 men. Two of these plants were assigned to each division on the front. They were always in the condition ready for instant movement. If any part of the division was bombarded by mustard gas, the plants proceeded immediately to the area and established a station where all men exposed to the bombardment were given hot prophylactic baths and clean clothing.

The following procedure was followed at the gas hospitals. Patients were received in the de-clothing tent or ward where they were stripped and their heads clipped for the reason that it was found that long hair harbored the gas. Following this, they proceeded to the bathing room where they were bathed by experienced attendants, after which their eyes, noses and ears were irrigated with a solution of sodium bicarbonate. They were then assigned to wards. During the process of bathing, the patients had to be kept warm, especially those in a state of collapse or suffering from shock.

TREATMENT

The general treatment of mustard gas cases will be considered under the following heads:

1. Eyes.
2. Skin.
3. Respiratory tract.

Treatment of the Eyes.—Wash the conjunctiva with a solution of bicarbonate of soda, 2 per cent strength, then treat it with a little sterile oil. The eyes should be placed at complete rest thus relieving them from strain. Protect the eyes against strong light by confining the patient in a darkened room or by having him wear dark glasses. Avoid the use of any form of bandages or compresses, which may retain the infected secretions.

In washing the eyes, use a syringe or douche cup, opening the eyelids wide by inverting them, if possible, and paying particular attention to the condition of the cornea. If a mucopurulent discharge is present, a 2 per cent argyrol solution should be used as a wash once or twice daily. In many cases the most troublesome complications are usually the photophobia resulting from burns of the eyes. As a rule the only treatment required is protection against light.

Although the use of anesthetics is contra-indicated in eye troubles if the pain is severe, novocain in 2 per cent solution with the addition of 3 per cent adrenalin solution (1:1,000) may be used. Cocain should be avoided. In the latter stages of conjunctivitis, 5 drops of 0.5 per cent solution of zinc sulphate dropped in the eyes three times daily will give relief.

Treatment of the Skin Lesions.—After removal of the clothing, the body should be sponged with coal oil when possible followed by a hot bath with alkaline soap. Coal oil or kerosene was used quite extensively in France with excellent results.

The early experiments in working on the therapy of mustard burns had as their object the discovery of methods of treatment which would prevent the formation of blisters after exposure. This work was based on the principle that the mustard gas was still on the surface of the skin and that the agent used would combine with the substance and render it innocuous. Later, however, when it was ascertained that the gas probably acted by the intracellular liberation of hydrochloric acid, it became evident that any treatment to be of value would have to penetrate the skin and prevent to a degree the action of the gas. With this object in view, therefore, many substances were tried.

English investigators reported the following results:

Useless: sodium bicarbonate, ammonia, hydrogen peroxid, bleaching powder, formaldehyd.

Harmful: iodin.

Some benefit: carron oil, potassium permanganate, chloramine-T, aqueous silver nitrate 5 per cent.

It was found that chloramine-T used five hours after exposure did not prevent blistering, but did prevent to a great extent the development of the erythematous areas around the vesicles. It did not prevent the damage already done. When using chloramine-T as a treatment for gas burns, the affected part should be kept moist with a 1 per cent solution in 0.5 per cent solution of sodium chlorid and applied on lint. When the vesicle is full, it should be opened and the liquid squeezed out. The chloramine-T dressing should be continued for two to three days when it should be replaced by some protective preparation of dusting powder.

Dakin's solution has also been tried extensively, and in the mild cases of mustard burns has proved very satisfactory. When used, the parts should be washed with it, or better, immersed for two hours in strength of about 0.5 per cent hypochlorous acid. If too irritating, the solution can be diluted. If much of the body surface is burned, the solution can be used in the form of a bath, and for lesions of the genital organs a sitz-bath should be used. For ordinary burns, compresses of Dakin's solution or slow irrigation gives great relief.

Many ointments of various kinds have been used, but with little effect. Butyl salicylate ointment containing from 20 per cent to 60 per cent anhydrous wool fat and 25 per cent water relieves the irritation so troublesome in many of these cases, but it has no curative effect. Professor Angeli (Rome) reported favorably on the following ointment:

Manganese linoleate	50 gm.
Zinc linoleate	500 gm.
Linseed oil	500 gm.

The ointment, if applied immediately after mustard comes in contact with the skin, is said to prevent the formation of blisters, and if applied within two hours reduces the severity of the burns.

Treatment of Blisters.—Amberg, Austin and Helmholz recommend the following method of treating blisters: After opening the blister, a piece of rubber dam is placed on the anointed surface and folded back on a gauze pad, which serves as a protection. By this procedure, the granular surface is completely bathed in pus and the healing seems to be accelerated with the additional advantage of no thick adherent scab forming.

The burn and adjacent area is cleaned with alcohol or ether. The blister fluid is allowed to escape and adhesive strips one inch wide are applied over the surface. This dressing should be changed every two days or at longer intervals if there be no discomfort.

Wolfe paints the skin of the burned and adjacent areas with iodin, opens the blister with a sterilized needle and aspirates the fluid. The burn is then covered with a dusting powder of starch and salicylic acid.

Sollmann believes that the opening of the blister has little influence on the ultimate course of recovery. He believes that, if opened at all, it should be merely pricked, leaving the epidermis in place. This will serve to form a scab and in the meantime protect the surface against irritation. The unopened blisters appear to be much more comfortable than those in which the epidermis has been cut away.

Treatment of the Respiratory Tract.—The first treatment to be administered in these cases is for the relief of the cough which is always present either in a mild or severe form accompanied by a marked hemoptysis caused by the rupture of the smaller pulmonary vessels. If the respiratory condition can be controlled at the beginning, the danger of secondary infection is greatly lessened and convalescence is greatly shortened. For the edema of the uvula and fauces often present, a spray composed of phenol 4 parts, glycerin 30 parts, tannic acid 2 parts, and water 40 parts often gives relief.

In those cases with severe involvement of the larynx and trachea, the following has been found satisfactory: syrup of tolu 4 c.c., heroin .005 gm. In some cases it may be necessary to administer hypodermically small doses of morphin.

The ordinary expectorants are of little value. If the expectoration is purulent, the draining of the lungs and respiratory tract is suggested. This is best accomplished by the inversion of the patient—head downward from the hips. This can be done every four or five hours if necessary.

A subsequent bronchopneumonia following gassing should be treated in the usual manner. As mustard gas cases are very susceptible to respiratory infection, the pneumonia cases as they develop should be promptly isolated and all possible precautions taken to prevent the spread of the infection.

Nasal lesions should be treated by soda and saline irrigation followed by the installation of a few drops of the following: camphor 0.650, menthol 0.139, oil of cloves .1 c.c., liquid petrolatum ad 60 c.c.—two drops in each nostril three times a day.

PROGNOSIS

Few deaths result from the direct effects of mustard gas. When they occur, they are generally due to a secondary infection. The conjunctivitis, one of the most troublesome conditions, responds readily to treatment, and as a rule clears up in from three to four weeks. A few of the more obstinate cases, however, may take longer.

All laryngeal trouble generally disappears in from two to three weeks, but a functional aphonia may last some weeks longer. Bronchitis usually clears up in from ten days to two weeks. The skin lesions are slow in healing, the extension of the burns governing each case. As a rule the average gas cases are fit for duty in from three to six weeks. The staining of the skin gradually disappears in from three to four months.

There are no serious organic effects of the stomach or kidneys. In some of the more severe cases with excessive burns some kidney involvement may be present.

PHYSIOLOGICAL ACTION OF TEAR GAS AND TREATMENT THEREOF

Action.—The immediate effect of a trace of the vapor of a lacrimatory gas, or tear gas, in the air is profuse watering of the eyes, accompanied by smarting. If the concentration is great, the smarting and pain in the eyes may become intolerable, rendering it impossible to keep the eyes open.

With increased concentrations of the vapor other effects may become manifest, especially irritation of the upper respiratory passages, accompanied by a burning sensation in the throat and coughing. Nausea is also often present, which frequently leads to vomiting accompanied by pain in the epigastrium. Nervous symptoms, such as slight mental confusion and torpor, may also show themselves. After removal to pure air these symptoms entirely disappear with the exception, in some cases, of redness of the eyelids and slight conjunctiva, which may remain for several hours.

There are no subsequent toxic effects following exposure to tear gases. Those exposed will be fit to perform their ordinary duties as soon as the primary effects have passed off.

The majority of the lacrimators have an instantly powerful effect on the eyes at a concentration of one part in a million, or even less.

Treatment.—Those exposed to lacrimatory gas should be evacuated immediately to a gas-free atmosphere. In ordinary cases this will suffice, and the eyes will immediately recover.

On no account should the eyes be rubbed or bandaged; this only irritates them. Inasmuch as the hands are also contaminated with the gas, they may be the means of increasing the amount of infection in the eyes. After the hands have been thoroughly cleansed with soap and water, the face may be washed; this will remove any remaining sources of contamination.

Those who have been exposed to the gas should not enter enclosures, as the gas on their clothing will serve to gas those therein.

No treatment for nausea and other symptomatic effects is necessary, as these disappear upon removal to pure air.

PHOSPHORUS

Two forms of phosphorus are used ror war purposes: the white and red. Taken internally in small amounts they act as violent poisons and when coming in contact with the skin produce severe burns. A few hours following the ingestion of small doses of phosphorus, a sense of wretchedness, nausea, and severe abdominal pain occurs.

In severe cases, the vomiting continues from two to three days, generally followed by jaundice, headache, vertigo, delirium, convulsions, and, in severe cases, death. The degree of jaundice depends upon the amount taken into the system. The temperature generally ranges from 99½° to 102°, dropping to subnormal just before death.

The urine is scanty, of acid reaction, high specific gravity and contains bile, bile acid, albumin, and evidences of epithelium destruction. The pulse is rapid and very irregular; paralysis of the heart is liable to occur at any time.

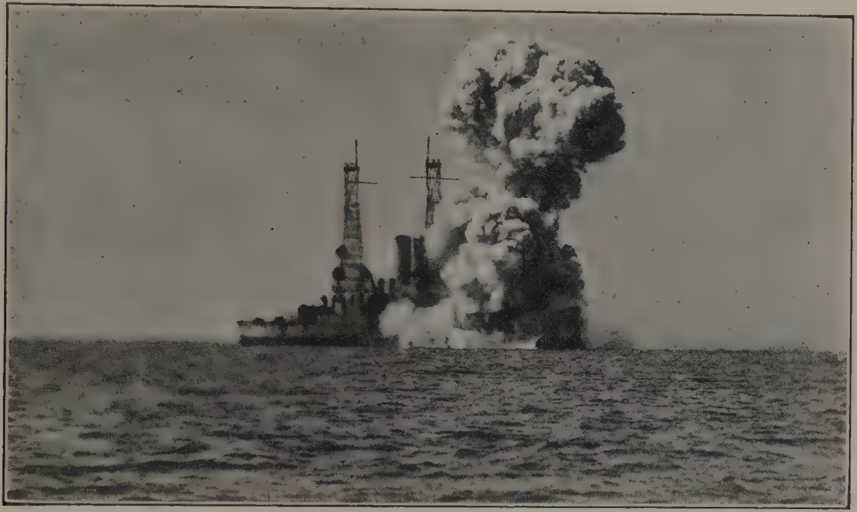

Fig. 9.—The Battleship Alabama Enveloped in Phosphorus-Smoke Dropped from Aeroplane at Elevation of 3,000 Feet.

Treatment.—Remove the patient to non-contaminated atmosphere and try and free the system of the poison. The administration of copper sulphate acts as a chemical antidote; .6 gm. in divided doses every five minutes should be given until free vomiting occurs. (Fig. 9.)

Phosphorus Burns

Phosphorus burns, often spoken of as "spattering wounds," are considered in the same category with burns caused by acids and alkalis and are of a tenacious character. The cellular elements of the tissues with which phosphorus comes in contact are destroyed with the formation of ulcers and sloughs. Healing does not take place until the sloughs entirely disappear which generally requires two to four months.

With severe burns, shock is always present.

Treatment.—The treatment of phosphorus burns taxes the skill of medical men more than any class of wounds in the realm of medicine. Shock and pain, if present, must be relieved—stimulants and salines being used for the former and opiates for the latter condition. The best treatment for phosphorus burns consists in cleansing the parts with hydrogen dioxid or some other mild antiseptic, and the application of rubber membranous tissue over the burn together with a thick covering of sterilized dressings.

The picric acid treatment has also proved highly efficacious for burns of this character.

AFTER EFFECTS OF WARFARE GASES

It was realized soon after the cessation of hostilities in the World War that the subject of the after effects of warfare gas was an important one, and to that end the medical services of the armies of the various countries which participated in the War started immediate investigations pertaining to the subject. In our own Government a Board of Medical Officers was convened at Fort Grant, Illinois, for the purpose of examining all cases of returning soldiers claiming disabilities from the effects of gas. This board was known as the Fort Grant Board, and during their session they carefully examined, individually and collectively, over two thousand cases, finally classifying them into the following groups:

The apparently normal group, which included about 50 per cent of the total. In this group a careful and thorough physical examination failed to reveal any abnormalities; expansion of the chest was normal, breath sounds were clear and vesicular, percussion note was negative, and there were no moist sounds. But, in the face of these apparently normal physical findings, the men complained of cough, shortness of breath on exertion, etc.

The bronchitic group, which included about 30 per cent of the cases examined. The findings in these cases were definite and did not differ materially from the subacute or chronic bronchitis that were early encountered. The type of breathing was harsh and high pitched throughout. Expiration was prolonged and at times interrupted, but most pronounced after exercise. Moisture in these cases was abundant. There were coarse, moist râles rather evenly distributed at the bases of the lungs.

The third group was characterized by the presence of emphysema. On expansion the chest seemed moderately rigid, the movements of the diaphragm limited; expansion was impaired and accessory muscles were thrown into use. On palpitation tactile fremitus was markedly diminished, and in some instances entirely absent. On percussion a hyperresonant sound was detected. On auscultation the breath sounds throughout the entire chest, except the bronchial areas, were much diminished.

After a general review of these cases by the Board, its findings were as follows:

That gas victims, irrespective of the type of gas and the severity of the attack sustained, showed no marked predisposition toward active pulmonary tuberculosis, or toward the reactivation of a healed or quiescent pulmonary lesion.

That gas victims presented little evidence of material destruction of lung tissue.

That gas victims with emphysematous symptoms had a more protracted convalescence than those of the bronchial group.

Notwithstanding the report of the Board, in whose findings other medical men who had given the subject much study concurred, many ex-soldiers claimed physical ailments due to tuberculosis and other respiratory diseases which they attributed to the effects of gas.

Since warfare gas was introduced as a surprise weapon, contrary to the established military rules of warfare, it has had a very unsavory reputation, which naturally gave it wide publicity. Again, the vast amount of press attention given it before, during and since the War has lent a romance to it such as has never before been associated with any weapon of war. The results produced by it have been greatly exaggerated. It is credited with more dire iniquities than have ever been associated with any other war weapon. Public opinion has become biased—naturally so, considering the romance surrounding it, the misinformation concerning the types and degrees of wounds produced by it, and the progressive efforts on the part of a few who have intentionally presented the wrong phases of the subject. The result has been a curiously illogical attitude of mind on the part of a large number of people.

Warfare gas has become almost a fetish. To what extent it should be held responsible for a great train of symptoms of which so many ex-soldiers complain is an open question, and one requiring a solution. On gas has been placed the blame for every conceivable sort of ailment. There is scarcely a functioning organ of the body whose disturbed action at some period has not had gas poisoning as a suggested cause.

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CHAPTER XLII

FOOD POISONING FROM INHERENT AND PUTREFACTIVE POISONS

William W. Ford

A number of different articles of diet containing fairly well-known poisonous principles of definite chemical composition which are the product of the metabolism of the plant or animal consumed are poisonous to man on ingestion. Other articles of diet become poisonous as a result of the growth in them of higher fungi which produce poisonous substances. As examples of the first group we have the poisonous mushrooms which owe their toxicity to certain poisons which are elaborated by the plants themselves. As an example of the second we have rye or other grasses which become infected with a particular fungus, producing a poisonous principle as it develops on the grain, this poisonous principle being responsible for ergotism, a serious disease in Europe. Finally we have a third kind of poisoning which results from the use of food materials which have decomposed as the result of bacterial action. To this name "ptomain poisoning" has usually been applied in the past. The ptomains are derivatives of proteins which occur in decomposed foods and which are supposed to represent the poisonous principles. As an example of this type we have poisoning from milk and its products ice cream and cheese, and from decayed fish and shellfish. The more completely epidemics of food poisoning of this character are studied, the greater is the amount of evidence that the cause of the illness is in reality the bacteria which are present in the food and produce infection when the food is taken into the alimentary canal. In other words, food poisoning is in reality infection from food contaminated by bacteria. How far we must discard the old idea that decomposed food is of itself capable of causing poisoning apart from the action of bacteria which bring about the decomposition is by no means clear to-day. In addition we have occasionally poisoning from foods which contain inherent poisonous principles in small quantity but which also may have been spoiled at the time of consumption. In such instances it may be impossible to say whether the poison originally present in the plant or the substances evolved from bacterial action are responsible for the symptoms shown on ingestion. This type of poisoning is represented by potato poisoning, which is comparatively rare. In this section on food poisoning we will discuss ergotism, potato poisoning, rhubarb poisoning, and poisoning from milk, fish and shellfish, and from mushrooms.

MORE COMMON FORMS OF FOOD POISONING

From early times epidemics of disease with peculiar symptoms have occurred in Europe and have been attributed to the use of foods containing flour made from diseased rye, wheat, oats, etc. At certain times the spores found in the asci of a small fungus, Claviceps purpurea, are deposited on the young seeds of the plants and develop a mycelium of long, spindle-shaped, furrowed bodies dark violet in color. The consumption of flour made from the diseased plants, chiefly rye, leads to the disease known as ergotism. Epidemics of ergotism were very common in Europe in the sixteenth, seventeenth and eighteenth centuries. In 1867-1868 a severe epidemic occurred in East Prussia, one in 1894 in Nanterre, France, one in 1907-1908 in Hungary, and in various years smaller epidemics in Russia (Kobert). Ergotism does not occur in America.

Clinical Symptoms.—Ergotism following the use of flour made from plants infected with Claviceps purpurea manifests itself under a great variety of symptoms. It is usually described as *spasmodic* or *convulsive ergotism* and *gangrenous ergotism*, since epidemics usually show one type or other of intoxication. In certain epidemics, however, both types of disease have occurred.

Ergotismus Spasmodicus or Convulsivus.—According to Meyer and Gottlieb this type of ergotism begins with a feeling of numbness in the fingers and hands which spreads over the whole body. Disturbances of the alimentary canal soon set in—vomiting and diarrhea. Finally typical cramps develop—very painful tonic contractions of the muscles. They affect especially the flexors of the extremities and lead to characteristic contractures. Clonic epileptiform convulsions then appear which are extremely painful and may last for several hours. The contractures of the flexor muscles are permanent and result in marked deformities. Finally the nervous system is affected, a kind of pseudotabes or imbecility developing.

Ergotismus Gangrenosus.—This type of intoxication begins in the same way with numbness and prickling of the fingers, vomiting and diarrhea. After a few days a peculiar dry gangrene sets in affecting chiefly the fingers and toes, the lobes of the ears and the soft parts of the nose. The skin over the affected regions loses its natural color, becomes blue-black and the epidermis is raised from the underlying tissues. Eventually a considerable loss of tissue takes place. The gangrene is accompanied by sharp pains in the early stages but later by a complete loss of sensation.

In the early stages of ergotism of both types, premature births and abortions are common. The recognition of this action of ergot led to its extensive use as an oxytoxic, and eventually its employment was forbidden by law.

Active Principle.—Crude ergot has a threefold action. The first is that of exciting spasms and is responsible for the *convulsive ergotism.* The second is that of causing gangrene and is responsible for the *gangrenous ergotism.* The third action is that upon the uterus. In addition vasoconstriction and a rise of blood-pressure are caused experimentally in animals by active extracts of the drug. From time to time laborious attempts have been made to obtain the substances responsible for any or all of these activities of ergot. From the modern point of view ergot is a very complicated mixture of substances of which only three have been obtained pure and have physiological properties. The first of these, ergotoxin, according to Kraft, Barger, Carr and Dale, is the active principle and is specific for ergot. It is an amorphous alkaloid soluble in water with great difficulty. The other physiologically active substances, according to Barger and Dale, are water-soluble ptomaine like bases which either arise in the metabolism of the plant or are the result of bacterial action. Recently Spiro has obtained from ergot a crystalline base *ergotamin* which has all the physiological action of ergot. The amorphous ergotoxin is possibly a decomposition product of ergotamin, the active principle.

Treatment.—Treatment of ergotism is at best unsatisfactory since by the time symptoms appear the poisons have already combined with the affected tissues. In the beginning of the attack large doses of purgatives like calomel are indicated in the hope of causing some elimination of the drug through the intestines. Surgical procedures apparently have not been tried out to any degree but would seem to be advisable for the relief of the permanent contractures. In the gangrenous variety the affected tissue may be removed by operation, but in general the actual loss of tissue from the gangrene is not as great as is expected and there is some danger that more tissue may be removed than is necessary (Kobert).

Potato Poisoning

From time to time epidemics of food poisoning have occurred which on the basis of more or less insufficient epidemiological evidence have been attributed to the consumption of potatoes either normal or spoiled or diseased in some way. According to Savage one of the earliest outbreaks in Great Britain was described in 1846 by Banks. In this outbreak four members of a family of seven individuals were attacked with severe abdominal pain, constipation, tenderness and pain in anus and rectum, nearly complete suppression of urine and collapse. The illness was ascribed to the use of potatoes which were covered with black spots—possibly of decay. Such epidemics have now only historical interest to us as indicating the source of the usual belief that potatoes may be a cause of food poisoning. Modern instances of potato poisoning have been reported at length by Cortial, in 1889, who has described an outbreak affecting 101 soldiers, and by Schmiedeberg, in 1895, who has described four outbreaks among soldiers in garrison, one involving 357 individuals, one 90, one 125 and another 43. In the total 716 there were no deaths. Still more recently Pfuhl, 1899, described an epidemic in which 56 soldiers were affected, salted potatoes being regarded as the cause of the illness. Dieudonné, in 1904, has reported a somewhat similar outbreak at Himmelburg in 1903 involving from 150 to 180 soldiers who developed severe gastro-intestinal symptoms, vomiting, diarrhea, headache and collapse two hours after eating a dinner in which potato salad was served. A much more definite instance of poisoning which can be attributed to potatoes is that recently studied by Harris and Cockburn (see Savage, page 145). In November, 1917, 61 persons in Glasgow were attacked, of whom a child of five years died. The attacks lasted from a few hours to from two to three days with symptoms of headache, vomiting, diarrhea and debility. The fatal case died of strangulation of the bowel thought to be due to the extreme retching and vomiting. The only article of diet which was eaten in common by the affected individuals was potatoes. More recently Roth has studied an outbreak in Leipzig which is the most characteristic and convincing. Here 14 persons were affected with very severe abdominal pain, vomiting and diarrhea about an hour after eating potatoes both raw and cooked.

Potato poisoning is practically unknown in America.

Etiology of Potato Poisoning.—We have no certain knowledge of the underlying factors by virtue of which potatoes may become poisonous, but two explanations have been suggested. In the first place potatoes under normal conditions contain *solanin,* a peculiar poisonous principle resembling saponin and often described as a glucosidal alkaloid. Solanin is the active principle of deadly nightshade, Solanum nigrum and of bitter sweet, Solanum dulcamara. The berries of such plants are intensely poisonous on ingestion and are not uncommonly the cause of fatal intoxication in young children who eat them inadvertently. According to Mann, 1908, the chief symptoms are vomiting and diarrhea, pain in the stomach, cramps in the legs, with clonic spasms, dilatation of the pupils, pallor, coldness of extremities, collapse, hallucination and coma. Under normal conditions the potato, Solanum tuberosum, belonging to the same group as nightshade and bitter sweet, contains an appreciable amount of solanin. According to Meyer, 1895, the solanin content varies with the season, being 0.04 gm. per kg. in winter and 0.116 gm. in summer. The highest content he found was 1.34 gm. per kg. in sprouting and diseased potatoes. The poisonous dose of solanin for man is about 0.2 to 0.4 gm. of the isolated drug (Rothe) and it is difficult to see how the small quantities of solanin in potatoes can give rise to the serious poisoning which undoubtedly occurs. It is believed by some authors that under certain conditions the amount of solanin is greatly increased and is present in such quantity as to explain the poisoning which has developed. Thus Harris and Cockburn found potatoes in their epidemic which contained as much as 0.41 gm. per kg., regarded by them as from five to six times the normal amount. This is manifestly a much greater content of solanin than Meyer and others found, and may have been the cause of the illness. Much more striking evidence that solanin is the cause of potato poisoning is brought out by Rothe who found from 0.34 to 0.43 gm. of solanin per kg. in the same lot of potatoes as caused the condition. Since this is about ten times the normal amount we may safely conclude that its presence was the etiological agent in the epidemic.

More recently the presence of solanin in potatoes has been disregarded in the explanation of potato poisoning and the theory put forward that the potatoes which cause illness are decomposed and infected with specific microörganisms. Thus Dieudonné found that the potato salad was infected with Bacillus proteus and he regarded this organism as the cause of the poisoning. Rosenow has stated his belief that the usual cause of potato poisoning may be bacterial infection since potatoes are an excellent culture medium for organisms like Bacillus typhosus, Bacillus enteritidis of Gärtner, etc. There is much in favor of this point of view but the question is by no means settled. The carefully studied epidemic of Rothe would seem to incriminate solanin as the etiological agent in some instances.

Treatment.—In all instances of potato poisoning and especially in the solanin poisoning from deadly nightshade it is essential to rid the alimentary tract as early as possible of any toxic materials which may be present. This may be accomplished by large doses of calomel, salts, etc. Morphin in small doses is indicated to control the pain, but the essential thing is to maintain the body heat in the occasional collapse (especially in children) and to employ stimulants freely when necessary. For this purpose small doses of strychnia may be employed, digitalis to stimulate heart action, atropin, caffein, etc.

Poisoning from Rhubarb

Rhubarb or rheum, the root of Rheum officinale, contains a large amount of tannic acid and a cathartic probably a compound of oxyanthraquinone. In small quantities the constipating effect of the tannic acid is manifested. In large quantities the plant acts as a violent cathartic, producing sometimes a painful watery diarrhea. This is not usually accompanied by untoward symptoms and subsides spontaneously. Occasionally poisoning from oxalic acid has been reported as the result of eating the leaves or roots of the rhubarb plant (Doane).

Poisoning from Milk and Milk Products

Under ordinary circumstances cow's milk is one of the most valuable of our foods containing the various nutritive materials which are essential for a balanced diet and for the maintenance of health. Under certain conditions by no means well understood it may become poisonous to man on ingestion and give rise to serious illness and even death. This change in the character of the milk may be due to disease in the animals from which it is obtained or to the growth in the milk of contaminating bacteria which cause the development of poisonous substances.

Milk from Diseased Animals (Milk Sickness).—Milk from cows suffering from foot and mouth disease, tuberculosis of the udder, etc., is commonly believed to be poisonous to man on ingestion. Such milk harbors pathogenic organisms which are virulent to man so it is impossible to determine whether the poisonous effects are the result of the ingestion of the milk as such or the result of the infection set up when the pathogenic bacteria are introduced into the alimentary canal. Probably the only definite instance of milk containing poisons actually derived from the animal is that extremely interesting and now fortunately rare condition known as milk sickness associated with a disease of cattle and sheep known as trembles. Milk sickness and trembles were formerly very common in America, especially in North Carolina, Kentucky and Tennessee and in parts of Indiana and Illinois. In trembles of cattle, in which species only it has been adequately described, the onset is noticeable. The animals begin to mope and droop, walk more slowly than normally, falter in their gait and are obstinately constipated. The eyes are red and injected. They show extreme muscular weakness and tremble violently on muscular exertion. They are often very irritable and disposed to fight. This trembling stage is followed by exhaustion and paralysis. The animals have frequently a foul odor. They die of exhaustion. The milk and butter from cattle suffering from trembles is poisonous to man, producing a characteristic chain of symptoms. In acute cases the patients have prolonged violent vomiting, obstinate constipation, headache and excessive thirst with stiffness of the limbs. They may develop great weakness and debility, labored respiration, paralysis of the intestines and subnormal temperature. The breath sometimes has a garlicky odor. Death may occur in the acute stages or the patients may develop a subacute or chronic form of the disease known as "slows." Such patients are weak and languid, suffer from nausea and vomiting and palpitation of the heart. On muscular exertion they may also show the peculiar trembling pathognomonic of the disease.

The etiology of trembles and milk sickness has been much discussed. For years the belief was entertained in countries where the disease was endemic that it was due to pasturing cattle in certain areas where they could feed on poisonous plants. As a result of such feeding they developed an intoxication giving off the poisonous substance in the milk. A great many poisonous plants were suggested as the cause of trembles, including the white snakeroot (Eupatoreum urticæfolium), poison ivy (Rhus toxicodendron), Indian tobacco (Lobelia inflata), Indian hemp (Apocynum cannabinum), cowbane (Cicuta maculata) and poisonous mushrooms.

Comparatively few modern studies have been made on trembles and milk sickness. In 1909, Jordan and Harris made a careful bacteriological examination of animals dead of the disease and suggested that a pathogenic spore-bearing bacillus, Bacillus lactimorbi, might be the cause of trembles which would then be an infection and not a food intoxication. In 1917, Curtis and Wolfe and also Marsh and Clawson called attention to the abundance of white snakeroot (Eupatorium urticæfolium) in the moist shaded rich pasture lands where the grazing of cattle seems to give rise to trembles. They showed experimentally that cattle and sheep fed upon this plant developed trembles and often died of the condition. Finally Sacket was able to poison rabbits acutely by the oral administration of an alcoholic and an ether-chloroform extract of this plant.

The subject of trembles and milk sickness requires further investigation before its etiology is cleared up.

Milk sickness is now so rare in America that the physician is not often called upon to treat cases of this character except in some of the outlying country districts of the Middle West. When cases do occur it is essential to bear in mind that milk sickness is an intoxication arising from the absorption of poisons through the alimentary canal and that in many instances the acute symptoms subside and a chronic intoxication develops, pointing to a continued absorption of poisonous materials. It is necessary to remove this source of trouble by complete change in the patient's diet, especially as regards milk, butter and meat which might come from sick animals. In the acute stages it is imperative to relieve the obstinate constipation and to empty the gastro-intestinal tract as completely as possible by free catharsis. In the chronic cases the patients need proper nourishment, tonics, and complete freedom from muscular exertion until the poisonous substances are eliminated from the body.

Decomposed Milk.—Occasionally attacks of food poisoning with gastro-intestinal symptoms, vomiting, diarrhea, severe cramplike abdominal pain and collapse have been attributed to the consumption of milk which has undergone putrefactive decomposition. This type of food poisoning is usually spoken of as galactotoxism. It was formerly much more frequently reported than at present. A characteristic outbreak has been described by Vaughan. Here 4 individuals were seriously poisoned by milk, 3 of the patients dying. The outspoken symptoms were vomiting, great prostration, stupor, rapid and weak pulse, slight dilatation of the pupils of the eyes, rapid respiration, difficulty in deglutition. Other instances of milk poisoning have been reported by Newton and Wallace, Schearer, Firth and Camman.

In these instances of milk poisoning it is usually believed that highly virulent substances were developed in the milk as a result of peculiar or excessive bacterial contamination and from some of the samples the poisonous ptomain tyrotoxicon, discovered by Vaughan in cheese, was isolated.

Among milk products cheese and ice cream are not infrequently the cause of food poisoning. A typical outbreak of cheese poisoning was reported by Wallace and Doolittle. In this outbreak some 50 individuals were affected. The symptoms came on from two to five hours after eating the cheese and consisted of vomiting and diarrhea, vertigo, chills with pain in the epigastrium, cramps in the feet and legs and marked prostration. This poisoning was also attributed to tyrotoxicon. Cases of poisoning from ice cream have been reported by Vaughan and Novy and Schearer, who found tyrotoxicon in numerous samples, and by Vaughan and Perkins who obtained another highly toxic heat-resistant substance from the material examined.

At the present time the instances of poisoning from milk and milk products (apart from milk sickness) are usually explained on the basis of bacterial infection, our earlier conception of ptomain poisoning having been largely discarded in favor of the view that individuals who are taken ill after eating these various products are usually suffering from typhoid fever, paratyphoid fever or Gärtner bacillus infection. It must be admitted that the more exhaustively so-called food poisoning is studied, the more it falls into this category. At the same time it should be remembered that of all foods milk and its products are most open to contamination by bacteria of all sorts and descriptions and offer the most favorable nidus for their development. Among the bacteria which are normally present in milk, resistant spore-bearing bacilli are always found, as was originally pointed out by Flügge, and spore-bearing anaërobes as was first shown by Brown. Under certain circumstances some of these bacteria multiply in milk and produce true toxins, as was shown by Ford and Lawrence for Bacillus welchii. It is entirely possible that other toxic or poisonous substances may be produced in milk as it decomposes and be the etiological agent in milk poisoning.

Treatment.—In poisoning from decomposed or infected milk the intestines should be freed from the irritating materials by means of purgatives, calomel or saline, and attention be directed to the patient's general condition. Efforts should be made to maintain the body temperature and stimulants should be administered freely. It must always be borne in mind, however, that the acute gastro-intestinal symptoms may represent only the first stage in infections especially from organisms like the typhoid bacillus or paratyphoid bacilli. The physician should be on his guard, therefore, and submit the evacuations to careful examination for the typhoid and the paratyphoid bacillus, and the blood to agglutination tests for these organisms. In general the possibility of Asiatic cholera may be eliminated since this disease does not exist in this country, such cases as do occur being caught at quarantine. As a matter of medical importance, however, it should be remembered that in a number of epidemics of cholera the first few cases were regarded as ptomain poisoning, the diagnosis of cholera being established only when a bacteriological examination of the dejecta was made.

Poisoning from Fish

Certain varieties of fish have been known from early times to be poisonous on ingestion, the condition being described as ichthyismus or ichthyotoxism. The flesh of the fish and the internal organs may contain virulent poisons as in the case of the poisonous tropical fish which harbors the substance known as fugu. Or the roe of edible fish may become poisonous during the spawning season as with Barbus fluviatilis. In addition to these types of poisoning, which will be considered in the section on Tropical Fish, illness may develop from the use of fish which under normal conditions are perfectly healthful but which are either decomposed or which are infected with bacteria pathogenic to man. Definite instances of this type of fish poisoning are somewhat rare, especially in America, and are becoming still more seldom with the enforcement of proper public health regulations. As characteristic outbreaks may be mentioned that studied by Arustamow and Konstanoff and cited by Novy, apparently due to four different kinds of fish, the outbreak reported by David from herrings, the ones described by Ulrich and Abraham from pike cited by Richardson, and the instance of poisoning from canned salmon given by Vaughan. In all these cases the patients exhibited symptoms typical of food poisoning, vomiting, diarrhea, abdominal pain, weakness, with occasional symptoms referable to the nervous system such as difficulty in deglutition, disturbances of vision. The symptoms came on from eighteen to twenty-four hours after consumption of the poisonous material and usually subsided in a week to ten days. Death was very rare in these outbreaks.

The etiology of these instances of fish poisoning is somewhat obscure. In some instances, as in the outbreak of 28 cases from eating pike reported by Abraham, the fish were infected by bacteria of the Gärtner group (Bacillus enteritidis) which, however, were not isolated from the stools of the affected individuals. This instance of fish poisoning may thus be correlated with poisoning from meat infected with Gärtner bacilli. In the cases reported by Ulrich also Bacillus paratyphosus B was isolated from the blood of 2 patients while positive agglutination tests for this organism were given by the blood of 4 other patients. In other instances, as in the cases reported by Arustamow, the fish showed no outward sign of decomposition but were heavily infected with various types of intestinal and putrefactive bacteria, especially Bacillus coli and Bacillus proteus vulgaris.

Finally we have the interesting observations of Konstanoff (cited by Novy) who studied the material from a sturgeon, the consumption of which was followed by the death of 2 individuals. The fish showed no living bacteria but had been salted up to 15.6 per cent NaCl. Konstanoff further showed experimentally that bacteria introduced into fish which were subsequently salted died out in short periods (twenty days). The poisonous properties of such salted fish must therefore be attributed to bacterial changes in the fresh fish as a result of which some kind of toxic substance is produced which survives the salting. It is difficult to bring such observations into line with the present explanation of all fish poisoning as infections.

Poisoning from Shellfish—Mytilotoxism.—Poisoning from shellfish such as mussels, oysters, lobsters and crabs is not very uncommon, the cases exhibiting a great variety of symptoms and differing markedly in severity. In some instances the patients develop a peculiar urticaria accompanied by a diffuse edema of the skin after eating fresh shellfish which show no signs of decomposition. Here apparently the individuals have a special susceptibility to some chemical substance in the shellfish, probably the peculiar lymphagogue normally present in crabs and first investigated by Heidenhain. This lymphagogue was obtained by Heidenhain from the fresh tissues of crabs and cannot be regarded in any sense as a decomposition product. In other instances, individuals develop almost the same type of intoxication after the consumption of certain shellfish, showing an extensive urticaria with widespread edema of the skin. These patients are not abnormally sensitive to shellfish, are often in the habit of eating them and show symptoms of intoxication only when the shellfish they eat happen to be spoiled or decomposed. We have no satisfactory explanation of the etiology of this type of shellfish poisoning but the lymphagogue normally present is evidently greatly increased under certain circumstances, possibly as the result of decomposition. This is further suggested by the occasional occurrence of vague gastro-intestinal symptoms which point to the presence of some substance which acts as an irritant to the gastro-intestinal mucosa. In both types of poisoning, that in which the patients have an abnormal susceptibility to Heidenhain's lymphagogue and that in which the symptoms follow the consumption of presumably decomposed shellfish, the urticaria and edema subside rapidly and in from two to three days the patients are restored to complete health.

Much more serious than these cases of urticaria and edema are the outbreaks of severe poisoning which follow the use of badly decomposed mussels or oysters. The well-known cases which occurred at Wilhelmshaven in 1885, observed by Schmidtmann and reported by Virchow, may be cited as examples of this type of poisoning. Here the illness came on in a few hours after cooked mussels (Mytilus edulis) were eaten, the symptoms being referable chiefly to the nervous system. They consisted of a feeling of constriction in mouth, lips and neck, burning prickly sensations in hands and feet, giddiness, restlessness and general excitation like acute alcoholism. The pupils of the eyes were dilated, speech difficult. These symptoms were followed by dizziness, nausea, vomiting, numbness of the limbs and a feeling of suffocation. In 3 instances death occurred in from three to five days after eating the mussels. In the other instances the patients developed abundant perspiration and drowsiness, sleeping off the effects of the poisons in a few hours. From the poisonous mussels concerned in this outbreak, Brieger isolated several so-called ptomains, one of which proved to be poisonous to animals, inducing the same symptoms as the boiled mussels produced in man. To this poisonous ptomain Brieger gave the name mytilotoxin.

A more recent instance of poisoning of this type was reported by Rolfe in 1904. Here 2 sailors ate mussels which had been gathered from sewage-polluted water, but which had been repeatedly washed and thoroughly cooked in several changes of water. Four hours after the mussels were eaten the patients began to be dizzy, were unable to stand, had slight abdominal pain with distention, mental excitement like alcoholic delirium and a feeling of constriction in the neck, with dryness of the throat. They had no fever. One individual died in six hours in delirium and syncope with paralysis of the respiration. The other recovered. In another outbreak referred to by Novy, 1 patient died fifteen minutes after a meal of boiled mussels.

This type of shellfish poisoning has also been traced to the consumption of oysters, as in the instance reported by Brosch. Here one evening a man ate oysters which were known to be polluted and which had a bad taste. The next day he was sick with a severe headache and a pain in the side. He developed difficulty of speech, salivation, cyanosis, inability to walk and inability to void urine. The pupil of his right eye was dilated, ptosis of the lid developed, deglutition become impossible. He died of paralysis of the respiration within twelve hours after eating the oysters. At autopsy the liver was fatty, the heart muscle and kidney epithelium showed parenchymatous degeneration. No poisons were found in the body and no bacterial infection of the organs.

We have no accurate knowledge of the etiology of this type of shellfish poisoning. It is known that in some instances the shellfish have been gathered from sewage-polluted waters and it is generally assumed that some type of bacterial decomposition has taken place in them as a result of which virulent poisons are produced. It is significant that these poisons are heat-resistant and withstand thorough cooking.

A third type of shellfish poisoning occurs in which the symptoms are referable to the alimentary canal. They consist of vomiting, diarrhea, abdominal pain and come on several hours after eating the shellfish. This type of mytilotoxism corresponds to the ordinary type of food poisoning and is not usually severe. We know nothing of its etiology.

Finally it may be noted that there is a widespread popular belief in America that poisoning from decomposed lobsters and both hard and soft crabs is apt to be serious and sometimes fatal. Actual case reports to verify this belief are lacking.

Treatment.—The treatment of fish poisoning and shellfish poisoning must follow general lines. It is essential to empty the stomach and intestines thoroughly by lavage and free catharsis, to use stimulants early and maintain the body temperature, to watch the action of the heart carefully and use cardiac stimulants early and repeatedly. In acute heart failure direct injection of such drugs as strophanthin into the circulation or even the heart muscle may have to be employed. As in other types of food poisoning the physician should remember that the acute symptoms may represent the onset of infection with some such organisms as the typhoid bacillus, the Gärtner bacillus or the paratyphoid bacillus. The stools should be subjected to careful bacteriological examination, blood cultures be taken and the blood examined for agglutinins against a number of organisms. Finally it is well to bear in mind that acute methyl alcohol poisoning may simulate severe food poisoning. This is illustrated by the severe outbreak of methyl alcohol poisoning some years ago in Berlin. Here the first few cases reported were regarded as meat poisoning due to the Gärtner bacillus. Only when the cases continued to come to light was it finally shown that they had all originated from the use of cognac containing methyl alcohol and served in a particular dramshop.

Mushroom Poisoning

Well over a thousand species of mushrooms or fungi are edible and a considerable number of these, the meadow mushroom, the puffballs and the morels, are in common use in America. Certain types of agarics, such as Agaricus campestris, the meadow mushroom, are now cultivated in quantity and are offered for sale in the markets of nearly all our larger cities especially along the Atlantic seaboard. In a few states such as Pennsylvania and Ohio the mushroom industry has attained large proportions and hundreds of thousands of dollars are invested in it. Mushrooms are valued chiefly for their delicious taste and aroma and in consequence are employed principally as dietary accessories. Their use, however, is by no means confined to those who purchase them in the markets. During the summer months collectors scour the woods and fields looking everywhere for the edible varieties and the past ten or fifteen years have seen their use increase greatly. This is partly due to the organization of several clubs such as the Boston Mycological Club which has had regular exhibits of edible fungi during the warm season, has greatly stimulated interest in this subject in New England and has been the means of disseminating accurate knowledge throughout the United States. At the same time the Department of Agriculture in Washington has had several well-known experts at work on fungi and our scientific knowledge of them has been made much more exact.

Serious poisoning from mushrooms arises without exception from mistaking the poisonous forms popularly known as "toadstools" for the edible forms and occurs almost entirely among collectors. There are only a few instances of poisoning from mushrooms purchased in our markets. In some cities competent market inspectors are at hand to decide upon the character of those offered for sale, but the real cause of our lack of poisoning from purchased material lies in the fact that *market* mushrooms are almost without exception *cultivated* mushrooms. Only a few species are capable of artificial propagation and in general the "spawn" used in the beds for their propagation is the mycelium of Agaricus campestris, the meadow mushroom, or a very closely related species. Rarely other forms may grow in these beds and one or two cases of poisoning have arisen from the inclusion of a few poisonous plants in a lot of market mushrooms. No serious instances of poisoning of this character and no fatalities have been reported from this cause. Sometimes mushrooms are purchased by hotels and clubs from indiscriminate collectors and an occasional case of poisoning may be traced to the failure of proper identification. The practice of buying fungi from any but well-recognized sources is always fraught with danger and should be avoided. Mushroom poisoning arises almost entirely from the use of forms which under normal circumstances contain substances injurious to man on ingestion. Rarely edible forms may be decomposed when eaten and produce a mild type of food poisoning. Such cases are rare and not attended with fatalities. Contrary to our earlier belief the number of poisonous fungi or toadstools is quite large. It was formerly taught that practically the only poisonous species were the white-spored amanitas, Amanita muscaria and Amanita phalloides. The experience of recent years, however, and especially the more or less careful laboratory examination of a large amount of material, has shown that there are many other poisonous forms. At the same time during the late War, owing to the food scarcity, mushrooms were used in great quantity and variety in Central Europe and cases of poisoning were common both from well-known species and from species not previously used as food which proved to be poisonous. Recent reports in the European medical journals have given us quite a new point of view as to the number which are harmful, and as to the type of lesions in individuals dying from mushroom intoxication. Altogether there are about 80 species or varieties which either have been found poisonous to man, or which on laboratory examination have been shown to contain poisonous ingredients identical with those in our well-known poisonous species. A few of these will be considered here as examples of types of mushroom poisoning which the physician must recognize. The disease is rare in America as compared with illness from other causes such as the infections. As a type of food poisoning, however, it may be regarded as very frequent. Probably a hundred deaths occur every year and several hundred cases. The total number is thus more than the number of cases of food poisoning from any other cause. Only a few of the cases are ever reported in medical journals but the lay press gives accounts every summer of families which have been poisoned from toadstools. The number of cases has increased markedly in this country within the past few years owing to the large influx of immigrants from Central and Southeastern Europe. These people are familiar with fungi in their own country and gather poisonous species which in America resemble the edible species of Europe in habitat, color and size. At the same time every summer brings to light a few cases among those collectors who insist on trying out new varieties or varieties not clearly identified and who suffer the consequence of their temerity. The identification of mushrooms is difficult except for an expert botanist, the classification depending in the main upon the color of the spores.

Poisoning with Choleriform Symptoms.—By far the most frequent cause of mushroom poisoning, especially of the severe type with a high proportion of fatalities, is Amanita phalloides. This is known usually as the white or deadly amanita. It grows in the woods during the entire summer from early June to late October but is more abundant in August and September. It varies in height from 3 to 8 inches, is white in color, except for the upper surface of the top or pileus which may be smoke-colored, grayish, pale yellow or greenish. The under surface of the pileus is provided with a series of gills, also white, which are covered with white spores. The lower end of the stalk lies in a peculiar expansion which is known as the poison cup. This is often deep in the ground and the plant may sometimes be gathered without the realization that this cup is present. A smaller form of Amanita phalloides, Amanita verna, is pure white and is popularly known as the "destroying angel." This was originally described as a spring form but we now know that it grows during all the warm weather.

In poisoning by Amanita phalloides the symptoms come on in a few hours, from eight to ten. They are ushered in by violent attacks of vomiting and diarrhea with intense cramplike pains in the abdomen. This violent initial attack lasts from two to three hours after which the symptoms ameliorate only to return after a remission of from six to eight hours. The succeeding attack is apt to be more severe than the primary one, the pain being almost unbearable, the vomiting and diarrhea almost uncontrollable. In the fatal cases periods of remission alternate with severe attacks of pain, the diarrhea keeps up and various other symptoms develop. They may relate to the nervous system, consisting of convulsive movements or characteristic convulsions, twitching of the muscles of the face and limbs, rarely pupillary changes. The extreme suffering brings on a peculiar hippocratic facies known as "la face vulteuse" and seen almost without exception in the fatal cases. Renal symptoms are common, much more so than originally supposed. The urine is scanty and contains albumin and casts. Renal function tests indicate only a small secreting power left for the kidney tissue. Not infrequently complete anuresis develops. In fatal cases death may occur after from three to five days. In other instances chronic intoxication develops, the patients dying in from four to six weeks, usually of nephritis. In the cases which recover, the initial attack of vomiting, diarrhea and pain is not followed by secondary attacks, the patients gradually improve and are slowly restored to health. The mortality of Amanita phalloides poisoning is high. The plants have an excellent taste and are often eaten in large quantities. In some instances every individual who partakes of the meal containing them may die. In other instances smaller quantities are eaten and the individuals recover after the initial attack. The severity of the intoxication bears a definite ratio to the amount of poison ingested, except that young children are particularly susceptible. Several instances are on record where small children have died in from two to three days from eating bread soaked in the juice of the cooked amanitas (Pfrom). Raw Amanita phalloides are intensely poisonous, people dying from eating small portions of a single plant (Plowright). Cooking does not destroy the poisonous properties of this species which is poisonous also to dogs and cats. About half the cases of Amanita phalloides terminate fatally according to the statistics gathered recently from large series of cases.

At autopsy the lesions in Amanita phalloides intoxication are characteristic. They have been studied recently with considerable care by Schürer, Fahr, Schmidt, Herzog, and Miller. They consist esentially of an intense tissue destruction followed by a deposition of fat. This fatty change is most noticeable in the liver, in which the fat is greatly increased so that the liver resembles the fatty liver of phosphorous poisoning. The kidneys are diseased, showing a necrosis of the epithelium of the various tubules and a marked deposition of fat. Similar necrosis and fatty deposit is found in both voluntary and involuntary muscles. The blood itself is not markedly altered but minute hemorrhages are everywhere present, on the surface and in the substance of liver and kidney, in the peritoneum, in the pleura, in the voluntary muscles and in the heart muscle. These hemorrhages are apparently due to the destructive action of the poison on the endothelial lining of the smaller blood-vessels. They are often quite marked in the vessels of the mucous membrane of the stomach and intestines and lead to considerable hemorrhages from the walls of the gut.

The active principle of Amanita phalloides is the amanitotoxin, a substance present in the raw and cooked fungi in considerable quantity (Ford). It may be extracted in aqueous solution and obtained in a certain degree of purity by precipitation with phosphotungstic acid. Its exact chemical composition has not been worked out satisfactorily but it is not a protein in the ordinary sense, not a glucosid or an alkaloid. According to Schlesinger and Ford it may be an indol derivative or an aromatic phenol. The amanitotoxin is poisonous to both rabbits and guinea pigs, producing lesions which are strictly comparable to those seen in man in fatal intoxication, particularly the cell degeneration, the fatty deposition, the minute hemorrhages. Various other substances are present in the plant, especially a certain hemolytic glucosid known as the amanitohemolysin, but this plays no rôle in the poisoning of man.

In addition to Amanita phalloides a number of closely related amanitas contain the amanitotoxin and are equally poisonous on ingestion. Poisoning with symptoms like those seen with Amanita phalloides is produced by only two other fungi Pholiota autumnalis and Hygrophorus conicus. Fatal cases from eating Pholiota autumnalis have been reported from Minnesota by Peck. The illness is serious and the reported mortality high. According to Ford and Sherrick this species contains poisons as powerful as the amanitotoxin. Hygrophorus conicus is regarded as a deadly poisonous mushroom in France. Fatal cases have also been reported from China.

Poisoning with Gastro-intestinal and Nervous Symptoms.—Next to Amanita phalloides the most poisonous fungus is Amanita muscaria, often called the "fly amanita" because decoctions of it have been used from early times for killing flies. Amanita muscaria is also usually regarded as a toadstool by ordinary collectors. It is a strikingly conspicuous plant appearing in the depths and along the edges of woods in the latter part of July, August and September. It is frequently larger than Amanita phalloides, growing sometimes to a height of 10 or 11 inches. The upper surface of the pileus is bright orange-yellow in the characteristic specimens and is covered with fragile white scales easily brushed off. The under part of the pileus is provided with white gills which are covered with white spores. The stalk is thick, often hollow and is also provided with whitish scales. The base of the stalk sits deeply in the ground, being attached directly to the growing mycelium, no poison cup being present.

Amanita muscaria is easily recognized even by inexperienced collectors.

Poisoning by Amanita muscaria was quite frequent in early times, before the poisonous constituents were thoroughly studied, and was frequently attended by fatalities. In recent years death from its ingestion has become very rare. During the period of the War, instances of poisoning from it were reported in considerable numbers from the eastern part of Germany and from the contiguous districts of Russia. In the latter country indeed Amanita muscaria has always figured as a cause of death owing to the use of "muscaria" decoctions among the Koraks to induce drunkenness.

In poisoning by Amanita muscaria the symptoms begin to appear from two to three hours after the fungi are eaten. They vary greatly in intensity and in characteristics. They may be ushered in by a violent attack of nausea, vomiting and diarrhea. The purging may be very severe and accompanied by intense abdominal pain. Incontinence of urine may ocasionally appear as well as salivation and lacrimation. Ocular symptoms are practically always present, the pupils being contracted and pin point. There is usually a profuse perspiration. After this preliminary attack the symptoms may subside completely in a few hours, the patient sinking into a profound sleep and awaking exhausted but otherwise well the next day. In other cases these preliminary symptoms subside and almost immediately symptoms arise indicating profound derangement of the nervous system. They consist of ocular changes, trismus, convulsions and coma. The convulsions may be extremely violent, in one classic case the bed upon which the patient was lying being broken by the patient's movements. The loss of consciousness is complete and the patient cannot be roused by any stimulus. Without treatment such a patient dies in a few hours.

In other instances, nervous system symptoms predominate from the beginning. After eating the mushrooms the patients have no feeling of discomfort or illness until they begin to experience a sense of dizziness, confusion of ideas, hallucination and difficulty in vision. They may now either become unconscious or begin to have convulsive movements and then well-marked convulsions. These symptoms are always accompanied by ocular changes, extreme narrowing of the pupils and occasionally trismus, together with a profuse perspiration. In this type of poisoning gastro-intestinal symptoms are frequently lacking.

The mortality in Amanita muscaria intoxication is now very low, several hundred cases having been reported in the past few years with no fatalities. This is due in part to the institution of early treatment and is in part due to the fact that Amanita muscaria frequently has a disagreeable taste in consequence of which only small quantities are eaten. The symptomatology shown by the various cases is explained by the action of the active principle. In the fatal cases the patients die of paralysis of respiration or extreme dilatation of the heart. At autopsy in "muscaria" poisoning there are practically no lesions. Occasionally hemorrhages into the intestines or into the peritoneal or pleural cavities have been noted. There is a complete absence of those pathological changes prominent in Amanita phalloides intoxication, such as the various cell degenerations and the deposition of fat.

The active principle of Amanita muscaria is muscarin first isolated by Schmiedeberg and Koppe and since found in all specimens of the plant which have been accurately identified. Muscarin was originally described as an alkaloid but it is now regarded as an ammonia derivative. It has the empirical formula $C_6H_{15}NO_2$. Pure muscarin produces experimentally in animals almost the same symptoms as are seen in man in "muscaria" intoxication. Within a few hours, from two to five, after subcutaneous administration the animals develop salivation, lacrimation, diarrhea and extreme narrowing of the pupils which fail to respond to light. Coincident with these symptoms the animals show characteristic convulsions and die in coma in from ten to twelve hours. At autopsy the only changes seen are the occasional hemorrhages into the alimentary canal and a greatly dilated heart. With intravenous inoculation the animals develop symptoms much more rapidly and may die from cardiac failure in a few moments. It has now been established by a large series of observation that atropin is a perfect physiological antidote for muscarin. This is best brought out by the observations on the isolated frog's heart. The application of muscarin causes an extreme dilatation and stoppage in a few moments. If now a dilute solution of atropin be applied, the heart begins to contract vigorously and shortly regains its normal rate. Further applications of muscarin have no effect. Besides muscarin the Siberian Amanita muscaria, according to Schmiedeberg, contains a substance acting like atropin and producing a dilatation of the pupil. This was named "muskaridin" by Schmiedeberg and subsequently renamed "pilzatropin" by Kobert.

In addition to Amanita muscaria, muscarin or closely related principles are present in a large number of other fungi, Amanita pantherina, Boletus luridus (Boehm), Boletus satanas (Utz), Inocybe infida (Clark and Kantor), Inocybe infelix (Ford), Inocybe decipiens (Ford and Sherrick), Inocybe maxima (Ford), and Inocybe lateraria (Fahrig).

The boleti are tube-bearing fungi which grow in the depths of the woods and are conspicous for their size, often quite large, and for their bright colors. In this country Boletus miniato-olivaceus has been reported as poisonous by Collins, producing vomiting, purging and prostration with narrowing of the field of vision. The inocybes are small plants of great interest to collectors. Several instances of poisoning have been reported from them, the symptoms suggesting muscarin intoxication. Muscarin is apparently also present in small quantity in one of the clitocybes, Clitocybe sudorifica, the ingestion of which occasionally induces profuse perspiration (Roberts).

Poisoning with Gastro-intestinal Symptoms.—Several mushrooms produce violent gastro-intestinal distress—severe abdominal pain, retching and vomiting and diarrhea. The best known of these are Russula emetica, Lactarius torminosus, Clitocybe illudens and Lepiota morgani. Russula emetica is a bright-colored fungus with white gills and spores which grows abundantly in the woods. It has a sharp bitter taste and small quantities produce persistent vomiting. Lactarius torminosus is almost the only mushroom with a milky juice which is poisonous. The majority are edible and one, Lactarius deliciosus, is a great favorite among collectors. Lactarius torminosus is intensely irritating to the gastro-intestinal mucosa, producing severe abdominal pain and profuse painful diarrhea. A somewhat similar effect follows the ingestion of Clitocybe illudens. This is a large plant, bright orange-brown in color, growing in clumps at the base of tree trunks. It has a peculiar phosphorescent glow at night and is frequently called "will-o'-the-wisp" or "jack-o'-lantern." According to Farlow and Fischer, its consumption is followed by free vigorous vomiting without diarrhea or special pain, lasting for a number of hours. Lepiota morgani is one of the few indigenous American mushrooms, growing especially in the Ohio Valley. It is a very large plant with green spores resembling certain edible lepiotas. Small quantities produce violent gastro-intestinal disturbance with vomiting and profuse watery diarrhea. Only one fatality has thus far been reported from it (Blount). Finally poisoning from the entolomas may be associated with this type of intoxication. The entolomas are small fungi with rose-colored spores which are seldom eaten in America. One species, Entoloma lividum, is definitely poisonous, a number of cases being reported from France. The French writers have described an entolomian syndrome (*syndrome entolomién*) in which vomiting, diarrhea, pupillary changes and syncope are the important symptoms.

Poisoning with Blood Changes.—Poisoning from the consumption of the "poisonous morels," Helvella or Gyrometra esculenta, was formerly very common in Germany, the active principle of this fungus being obtained by Boehm and Külz. It is a hemolytic or blood-destroying substance of an acid reaction named helvellic acid, which will reproduce in animals, dogs and cats, a type of intoxication like that seen in man. It is heat-resistant and easily removed from the fungi by soaking them in hot water. Helvella or Gyrometra esculenta is often accepted as an edible fungus provided it be first boiled in water and the first washings discarded. Our information in regard to it was based upon observation made some years ago and cases of helvella poisoning became almost unknown. Recently, however, quite a number of accidents from this species were reported from Germany and the symptomatology and pathology has been studied with great care by Lövegren, Umber, Henius, Lyon, Stahl, and Herzog. The symptoms come on slowly, usually about twenty-four hours after the fungi are eaten. They consist of jaundice and hemoglobinuria with occasional vague gastro-intestinal disturbances. These symptoms are seldom severe, passing off in a few days. Rarely death may occur from eating large quantities. At autopsy in such cases there is evidence of extensive blood destruction, manifested by marked pigmentation of liver, kidney and spleen. Poisoning from Helvella or Gyrometra esculenta is rare in America but cases have been reported from Canada and Michigan.

Poisoning with Cerebral Symptoms.—One mushroom Panaeolus papilionaceus produces peculiar cerebral symptoms. It is a small plant which grows in lawns and on heaps of manure in gardens. It is about the size of the ordinary meadow mushroom and has black spores. It may occasionally be mistaken for an edible species. Rarely it gets into mushroom beds where it is overlooked and a few specimens are gathered with a lot of market mushrooms. Poisoning from it is very characteristic. In a few hours the patients develop a type of intoxication in which disturbances of vision, difficulty in locomotion and hallucinations are the predominant symptoms. Occasionally there is a good deal of abdominal distress. A closely related mushroom Panaeolus campanulatus is said to produce the same type of intoxication.

Treatment.—With this characterization of cases of mushroom intoxication in mind, it becomes possible for the physician to establish a prognosis and institute measures of treatment even if he is unable to discover the particular variety of poisonous mushroom which has been eaten. The symptomatology of the cases is quite distinctive and practically every case can be associated with some one of the types of poisoning mentioned above.

In the choleriform intoxication due to Amanita phalloides, closely related amanitas, and Pholiota autumnalis and Hygrophorus conicus, the patients are seriously ill from the onset of symptoms and the prognosis is always grave, nearly one-half the cases terminating fatally. The stomach should be washed out thoroughly and repeatedly with salt solution and high enemata be given to remove the poisonous material from the gastro-intestinal tract. Atropin may be given at the outset on the chance that some of the fungi contained muscarin. Opiates are indicated to relieve the intense pain in the paroxysms and stimulants, strychnia, caffein and digitalis, whenever the heart shows signs of failure. The urine should be watched carefully for evidence of nephritis and diuretics administered and hot fomentations applied on the first evidence of kidney involvement. Even in the most serious cases it should be remembered that recent pathological studies indicate that in "phalloides" intoxication the damage to the liver and kidney is not beyond repair, and every effort should be made to tide the patient over the acute stage.

In poisoning with nervous symptoms, pupillary changes, delirium, hallucinations and convulsions, indicating that the mushrooms eaten contained muscarin (Amanita muscaria, etc.), we have a sovereign remedy in atropin, which is a physiological antidote. Atropin should be administered to this type of case as soon as seen, subcutaneously or intravenously. In cases apparently moribund from acute cardiac dilatation the atropin may be injected directly into the heart muscle. At the same time the stomach should be washed out and high enemata given to cleanse the gastro-intestinal tract of the poisonous material. Sometimes it may be advisable to administer apomorphia subcutaneously and purgatives as soon as the stomach can retain them. In general the treatment with gastric lavage and enemata is to be preferred. Atropin may be administered at fairly frequent intervals, together with digitalis and strychnia. In muscarin poisoning we have the type of case where vigorous watchful treatment kept up for long periods may maintain the life of the patient till the effect of the poison wears off. After recovery sets in, the prognosis is good, the patients being restored to complete health in a few days.

In poisoning with gastro-intestinal disturbances, vomiting and diarrhea, from Lactarius torminosus, Russula emetica, etc., drugs directed toward the gastro-intestinal tract are contra-indicated in the acute stages. The vomiting and diarrhea subside spontaneously and no effort should be made to check them. The patient's general condition should be watched carefully since old debilitated individuals and occasionally young children collapse. On the appearance of untoward symptoms, stimulants such as strychnia, caffein and digitalis should be employed. The prognosis in these cases is good.

In the rare instances of poisoning with blood destruction, as from Helvella esculenta, no line of treatment can be suggested beyond blood transfusion which apparently has not been tried. In intoxication with cerebral symptoms, as from Panaeolus papilionaceus and Panaeolus campanulatus, the symptoms wear off in a few hours. Nothing is needed beyond a good purge and rest in bed. The prognosis is good although rarely collapse has been noted.

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CHAPTER XLIII

POISONING FROM FOOD PRESERVATIVES AND DYES

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The preservation of food by addition of chemicals has long been practiced and it is probable that upon no other topic has a greater controversy been waged than upon the question of the influence upon health of the addition of these chemicals to food. In spite of the great amount of work that has been done upon the subject an actual demonstration is lacking that the addition of preservatives to food, as practiced, is harmful. On the other hand, it is granted that in sufficient doses these substances must be regarded as distinct poisons and occasionally, in circumstances other than from their use as preservatives, poisoning occurs.

So far as dyes or coloring matters are concerned some, such as annatto, employed to color butter, are believed to be entirely harmless, whereas others, for example the salts of copper and other metals, as well as various anilin derivatives, are either known to yield distinctly toxic effects or else are regarded with definite suspicion. Indeed, in many states of this country, and in European countries in general, specific laws are in force against their employment to color foods since these substances are classed as poisons.

Below is given a brief résumé of the toxicology of the most commonly employed food preservatives that are of interest in this connection. Our knowledge concerning the specific toxic action of anilin dyes as employed in foods is not sufficiently definite to allow a detailed account of the toxicology of these substances.

Poisoning from addition of salts of toxic metals is, however, different, a short review of the toxicology of substances usually employed being given below.

Boric Acid and Borax.—Both boric acid and borax have been extensively employed as food preservatives. One must assume that they exert an identical influence upon the nutrition of the body and as ordinarily consumed in small quantities occasionally there is little or no evidence that any deleterious influence is exerted. On the other hand there is no question concerning the continued use of even relatively small quantities of the substances for they tend to accumulate in the body, the digestion becomes somewhat deranged, body weight is lost, and the feces become more fluid without actual diarrhea being present. The effects may be even more detrimental for individuals with digestive or renal disturbances. Indeed, it has been shown that if an albuminuria is present it is increased under administration of food containing borax or boric acid. In general, borax and boric acid are excreted through the urine, little or none being eliminated by the bowel. When doses of from 1 to 3 gm. per day are ingested, pronounced effects follow so that it may be stated that doses of more than 2 gm. per day are distinctly harmful, the effects being seen mainly in gastro-intestinal and renal disturbances.

With acute poisoning from larger doses the following symptoms are to be observed: gastro-enteritis, nephritis, skin eruptions resembling those of scarlet fever, disturbances of vision, muscular weakness, lack of coördination, fall of temperature and collapse. On postmortem examination evidences of fatty degeneration are present rather generally.

Treatment.—Treatment of the chronic type of poisoning consists of preventing ingestion of these substances and measures to hasten elimination.

For acute poisoning, lavage of the stomach, catharsis, and stimulants are advocated.

Salicylic Acid.—Salicylic acid exists in combination in the volatile oils of birch and wintergreen and possesses about the same antiseptic powers as benzoic acid and phenol. It is irritant to mucous membranes and in strong solution effects destruction of the skin. It possesses a biting taste and distinctly retards gastric digestion. It is rapidly absorbed from the intestines and has analgesic properties resembling acetanilid in this respect. Rapidly excreted by all the secretions but principally through the urine, it leaves the body mainly as the salicyluric acid, a compound of salicylic acid and glycocoll. In large doses the urine may give a green color.

The toxic effects of salicylic acid, aside from the local irritant action, are characteristic of salicylates (see under Salicylates).

Benzoic Acid and Benzoates.—Benzoic acid occurs in the balsams, in cranberries, and in various vegetables and fruits. The free acid even in concentrations as low as 0.1 is distinctly irritant, whereas the salts are not. The toxicity of benzoic acid is low, due probably to its being transformed in the organism to hippuric acid by union with glycocoll which is readily excreted by the kidney.

Investigations by various governmental commissions have led to the conclusion that the presence of small quantities of benzoate in food is without evidence of harmfulness although in larger doses the conclusions do not appear to be so concordant. It is quite apparent that benzoate in food as ordinarily preserved may be taken by normal individuals without serious detriment. With patients with gastro-intestinal or kidney lesions the inherent irritant properties of the acid may prove deleterious.

In sufficient doses benzoic acid and its salts exhibit symptoms of toxicity strikingly similar to those of phenol poisoning. There is gastric irritation, nausea and vomiting. The respiration is dyspneic in character, the reflexes are diminished, and either coma or convulsions may ensue.

Treatment.—This form of poisoning is treated by evacuation, by lavage of the stomach, and by stimulants.

Saccharin.—Saccharin, or benzosulphinid, has an intensely sweet taste, even in greatly diluted solution. It passes through the body practically unchanged within a period of twenty-four hours, almost all being eliminated by the kidneys. It has a sweetness about five hundred times that of sugar and has been extensively employed to give a sweet taste to the food of diabetics and as an adulterant of sweet foods.

Although the older literature reveals reports of various digestive and other disorders following the use of saccharin, later work has all tended to demonstrate its low toxicity, although even here large doses tend to produce minor derangements. Distinctly poisonous effects in man are unknown.

Formaldehyd.—Formaldehyd at times has been employed as a food preservative, especially of milk, but its characteristic irritant properties render its employment in this connection extremely dangerous. When large doses have been swallowed, there is immediate agonizing abdominal pain, loss of consciousness and general collapse. Death usually occurs within forty-eight hours. Postmortem examination reveals acute and extensive gastritis. When death does not occur, the urine may be suppressed for twenty-four hours and usually when secretion is resumed the urine contains blood, albumin and casts. Sometimes there is diarrhea.

Formaldehyd is probably oxidized to formic acid, a part of which may appear in the urine.

Treatment.—Treatment of formaldehyd poisoning consists of lavage of the stomach and the administration of ammonia well diluted and ammonium salts, the formaldehyd thereby being rendered non-toxic by transformation into hexamethylen-tetramin. This should be followed by demulcents, such as bland oils, milk or white of egg.

Sulphites.—By the term sulphites is meant sulphurous acid, sodium sulphite and sodium thiosulphite. The substances are strongly reactive and readily combine with oxygen to form sulphates, which tends to render harmless their native toxicity. Even in large quantities this transformation into sulphates prevents a general systemic intoxication, their employment in food being associated with deleterious action because of local irritant properties through the liberation of sulphurous acid.

Systemic effects are in evidence only when quantities sufficient to overwhelm the oxidative capacity of the body have been ingested. Under these circumstances blood-pressure is lowered, there is central nervous depression and depression of the musculature of the heart and arteries. At times violent colic and diarrhea may be observed. Death results from paralysis of the respiratory center.

Treatment.—Treatment consists in evacuation of the gastro-intestinal tract by lavage and catharsis and general stimulation.

Nitrates.—Potassium nitrate, or saltpeter, has been and still is extensively employed in the preservation of meats. In general it acts like other neutral salts although it probably is distinctly more irritant to the stomach and intestine. Readily absorbed it is chiefly eliminated by the urine and has diuretic properties.

With large doses the characteristic symptoms include severe abdominal pain, vomiting and at times bloody stools. The pulse becomes irregular, convulsions occur and collapse ensues. The urine may be entirely suppressed or, if passed, may contain albumin and blood. Death may result from the gastro-intestinal disturbances provoked by the salt action.

Treatment.—Potassium nitrate poisoning should be treated by administration of large volumes of water and by gastric lavage. To allay the irritation of the gastro-intestinal tract, milk, eggs, etc., should be given.

Copper.—Copper in food is employed mainly for the purpose of giving a green color to peas and beans. It combines with the chlorophyl of young vegetables to form a stable compound, but with older vegetables the combination is not so firm. Consequently in the ingestion of these colored foods more copper gains entrance into the tissues when the older vegetables are eaten than when the young peas and beans colored with copper are taken. Even though the maximum quantities of the latter are eaten, distinct toxic symptoms are not in evidence. With large quantities of old vegetables colored with copper gastro-intestinal disturbances may occur.

The symptoms of poisoning are associated with the gastro-intestinal tract since copper is irritant and causes vomiting, diarrhea, and pain. Lesions in the kidney and spleen are characteristic.

Treatment.—Copper poisoning should be treated by the prompt administration of precipitants, such as white of egg, milk or acacia, with thorough lavage of the stomach, and stimulants if indicated.

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CHAPTER XLIV

THE TREATMENT OF ACIDOSIS OCCURRING IN CHILDHOOD

BENJAMIN KRAMER

Acidosis is a condition in which there is an accumulation of acid in the blood sufficient to lower its bicarbonate concentration or to cause a shift in its reaction toward acidity. Chemical processes in the living organism result in the formation of carbonic, sulphuric and phosphoric acids as well as of organic acids. Acids may also be introduced with the food. Eventually all of these find their way into the blood-stream. However, in spite of this constant influx of acid substances into the blood, the reaction of this fluid and its bicarbonate concentration are maintained at a constant level.

Nature of the "Neutrality Mechanism."—The studies of L. J. Henderson and others have shown that the ability of the organism to maintain a state of balance or equilibrium between acid production and elimination is due: (1) to the presence of certain substances in the blood, the so-called "buffer substances";[1] (2) to the ability of the lungs to excrete an acid (carbonic acid) as such, that is, not in combination with any basic element (Na, K, Ca, Mg., etc.); (3) to the production of ammonia from a neutral substance—urea; and (4) to the ability of the kidney to secrete an acid urine from an alkaline blood, and to excrete ammonium salts of acids.

For our purpose blood-plasma may be considered a solution of carbonic acid and sodium bicarbonate. When a non-volatile acid such as hydrochloric acid is added to such a solution a reaction occurs which is expressed roughly by the equation:

$$(1) \quad H_2CO_3 + NaHCO_3 + HCl = NaCl + 2H_2CO_3$$

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[1] A buffer solution is one containing a weak acid, such as carbonic acid and its salt, sodium bicarbonate. The reaction of such a solution can be adjusted so that it is only slightly more alkaline than water. The addition of a strong acid, like hydrochloric acid, produces only an insignificant change in the reaction of the buffer solution, whereas the addition of the same amount of acid to water produces a marked change; hence the term "buffer solution" to indicate its resistance to sudden changes in reaction.

Carbonic acid is formed at the expense of bicarbonate. Such a solution will attain its highest acidity when all the bicarbonate has been converted into carbonic acid. In a similar manner the addition of a non-volatile base will result in the formation of additional sodium bicarbonate, thus:

$$(2) \quad H_2CO_3 + NaHCO_3 + NaOH = 2NaHCO_3 + H_2O$$

The solution will attain its maximum alkalinity when all the carbonic acid has been changed into bicarbonate. Any reaction between these maxima may be obtained by adjusting the ratio of carbonic acid to bicarbonate. When this ratio is 1:20 the reaction of the solution corresponds to that of blood-plasma.

The addition of non-volatile acid to plasma uses up the bicarbonate and the liberation of additional carbonic acid disturbs the normal ratio of carbonic acid to bicarbonate and for a moment shifts the reaction of the blood toward acidity. This slight change of reaction stimulates the respiratory center and the pulmonary ventilation which follows not only disposes of the extra carbonic acid but an additional amount is excreted sufficient to balance the decrease of the bicarbonate. The normal ratio and the normal blood reaction are thus restored. However, this mechanism does not restore the bicarbonate concentration. Were this process to go on the blood would soon be depleted of its bicarbonate.

Long before an actual reduction of the alkalinity of the blood occurs other factors come into play to assist in maintaining a normal balance between acids and bases. Ammonia produced from the end products of protein metabolism unites with acids, forming ammonium salts which are excreted as such. Just where this union occurs is not yet clear. The union of ammonia with acid protects the body against loss of basic elements such as Na, K, Mg or Ca. This process is illustrated by the reaction:

$$NaCl + NH_4OH \rightleftarrows NH_4Cl + NaOH + CO_2 \rightleftarrows NH_4Cl + NaHCO_3$$

The chlorin of the sodium chlorid formed by reaction (1) unites with ammonia forming ammonium chlorid whereas the sodium thus liberated takes up CO_2 which is always available and $NaHCO_3$ is reformed. It is in this manner that ammonia protects the organism against loss of sodium and of *bicarbonate.* A further saving of fixed base (sodium, etc.) results from the ability of the kidneys to excrete an acid urine from an alkaline blood.[2] So efficient is this base-saving mechanism that even with fatal cases of acidosis there is practically no decrease of the concentration of base ($Na + K + Ca + Mg$) in the plasma, although the bicarbonate concentration may be reduced to about one-fourth of the normal amount.

Conditions arise in which the organism can no longer maintain a fixed balance between acid production and acid excretion. This may be due to an overproduction of acid as in diabetic acidosis or to a failure to excrete acid substances. The mechanism whereby ammonia is bound to acids may break down.

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[2] The actual amount of alkali conserved to the body may be determined by titrating the urine with 0.1 N sodium hydroxid from its observed reaction to that of the blood.

It has been known for some time that fats will be oxidized completely to carbonic acid and water only when an adequate amount of carbohydrate is simultaneously burned. This fact is expressed in the rather vague phrase that "fats burn only in the fire of carbohydrates." If the body is incapable of burning a sufficient amount of carbohydrate as in diabetes mellitus, or if the available supply is insufficient as during starvation or when a diet unusually rich in fat is ingested, ketone acids, such as hydroxybutyric and aceto-acetic, are formed in excess, accumulate in the blood and appear in the urine in increasing amounts. The older observations of Zeller, the recent experimental studies of Shaffer, and the clinical observations of Woodyatt have shown that significant amounts of ketone acids appear in the urine only when the amount of fat oxidized exceeds twice the carbohydrate plus one-half the protein. The accumulation of these acid bodies in the blood leads to a decrease of the bicarbonate concentration and to acidosis. Because the offending acids belong to the ketone acids the condition is known as ketosis. Other organic acids, notably lactic acid, may produce a similar condition.

An inability of the kidneys to perform their function of disposing of acids may likewise lead to the accumulation of acids in the blood and to a reduction of its bicarbonate concentration.

Diabetes Mellitus.—Walther first described as "acidosis" a condition which develops in rabbits during the administration of mineral acids. Not only did he observe hyperpnea but demonstrated a striking reduction of the blood bicarbonate. Kussmaul was first to recognize the similarity between the deep breathing of patients in diabetic coma and the hyperpnea which Walther had described several years before. For some time diabetic coma was the only clinical condition known to be associated with acidosis. Since the acidosis of diabetes is due to an overproduction of ketone acids, the terms "acidosis" and "ketosis" were for a time synonymous. More recent studies, to be discussed later, have shown that acidosis may occur in conditions where the existence of ketones cannot be demonstrated, so that the term "acidosis" is now applied to a condition occurring in various diseases which have in common a reduction of the concentration of blood bicarbonate, produced by the accumulation of nonvolatile acids.

Starvation.—Starvation acidosis in children has recently been the subject of a very careful study by Gamble and his associates. They found a marked increase in the ketone acids of the blood which adequately explains the decrease in the concentration of bicarbonate. No decrease of fixed base concentration (sodium, potassium, magnesium, and calcium) was observed. The administration of carbohydrate resulted in the oxidation of the retained ketone acids and a restoration of the bicarbonate to the normal level although no bicarbonate was administered.

Recurrent or Cyclic Vomiting.—Children suffering with cyclic vomiting often vomit almost continuously from the onset of the illness. They lose weight rapidly and become markedly dehydrated. With the loss of body fluids there is a loss of base, and, as shown by Marfan and others, there occurs very early a marked overproduction of ketone acids. These accumulate in the blood and appear in the urine and are responsible for the acidosis. A hypoglycemia seems to be a frequent finding with these patients.

Acidosis Associated with Acute Diarrhea, Dysentery, etc.—As early as 1897 Czerny called attention to the peculiar deep breathing of infants suffering with severe gastro-enteritis. He also recognized the resemblance of this type of breathing to that which occurs in rabbits poisoned with acid. Proof that this disturbance of respiration is due to acidosis was presented in 1914 by Howland and Marriott, and additional conclusive evidence was published by the same observers in 1916 and shortly thereafter by O. Schloss and R. E. Stetson.

The cause of this form of acidosis is as yet undetermined. Marriott is inclined to attribute it to the accumulation of lactic acid and of other organic acids in the blood. The studies of Marriott and Utheim have shown that the blood is concentrated, the circulating blood volume diminished, and the rate of blood flow in the extremities much reduced. These circulatory changes they believe lead to an inadequate supply of oxygen to the tissues and hence to imperfect oxidation. There results an overproduction and retention of organic acids. With many of these children oliguresis and even anuresis may be present. Since the kidneys normally excrete acids from the blood, it may be assumed that when this function is in abeyance these acids are retained and may be responsible for the acidosis. Marked dehydration is present in these children. It is not unlikely, therefore, that there is a loss of extracellular as well as of intracellular body fluid with its content of bicarbonate, so that the total capacity of the organism to neutralize acid is decreased. This decrease finds its reflection in the lowered bicarbonate concentration of the serum.

Acidosis Associated with Renal Insufficiency.—Renal insufficiency in children may be due to actual disease of the kidney itself or may be secondary to some other condition. Chronic diffuse nephritis with or without multiple cystic dilatation of the renal tubules has been described. This condition is associated with a high degree of functional insufficiency. Such children are usually anemic, undersized, undernourished, and rachitic. The condition has been called "renal dwarfism." The ability to excrete phenolsulphonephthalein is markedly decreased, the two-hour renal test shows fixation of the specific gravity at a low level, and an increase of the inorganic phosphorus can usually be demonstrated in the serum along with a decrease of the concentration of bicarbonate and of calcium. Hypertension may be present.

Burns, Eczema and Pyodermia.—Children with extensive burns may develop oliguresis or even anuresis. This may result in acidosis. A similar condition may occur with extensive eczema and pyodermia. Measures which bring about a resumption of renal activity will also relieve the acidosis.

Acetone and diacetic acid may be present in the urine, with many acute infections such as tonsillitis, dysentery, pneumonia, and scarlet fever. Acidosis may develop, but as a rule the amount of acid present in the blood is not sufficient to lower its bicarbonate concentration.

Clinical Diagnosis.—Acidosis is not a disease per se but rather a symptom resulting from an insufficiency of the mechanism concerned with the maintenance of the normal balance between acids and bases. The patient suffering with this condition is usually desperately ill and it is therefore necessary to establish the diagnosis of acidosis promptly so that proper treatment may be instituted, leaving for a later time the diagnosis of the underlying disease. The characteristic symptom of acidosis is hyperpnea. This form of breathing was first described by Kussmaul in patients in diabetic coma and has since been known as "Kussmaul breathing." To quote his original description:

> "Nothing indicates that the air on its way to or from the lungs has the least obstacle to overcome; the complete inspirations are followed by just as complete expirations. There is a lack of overfilling of the veins of the neck, of any cyanosis. This exaggerated respiration (*grosse Atmung*) is further, as a rule, accelerated. The contrast of the general weakness with the strength of respiratory movements is one of the most striking features of the picture."

Somnolence may be present and may gradually deepen into profound coma. Other symptoms, such as fever, marked dehydration, cyanosis, ashy pallor, persistent vomiting and marked prostration, often complete the picture. The hyperpnea of acidosis can usually be readily distinguished from the superficial breathing of pneumonia. With the latter condition a pause occurs during inspiration and is followed by an expiratory grunt. Physical examination of the lungs in pneumonia will usually reveal some suspicious or definite signs of consolidation, although the appearance of such signs may be delayed for several days. The periodic hyperpnea of epidemic encephalitis may be confused with the hyperpnea of acidosis. With cases of ketosis the breath may smell of acetone. Chemical tests for the detection of acetone in expired air have been described by Higgins and others.

In dealing with diseases in which acidosis is likely to develop one should not wait for the development of hyperpnea. A determination of the bicarbonate concentration of the serum (Van Slyke) will tell at once how imminent is the danger of acidosis and will lead to the institution of treatment when it is most likely to be effective. Improper handling of the blood may nullify the value of the most careful chemical analysis. The sample of blood should be collected under mineral oil with a minimum of exposure to the air. The loss of CO_2 which may occur if this precaution is not observed favors the migration of chlorin from the corpuscles into the serum. This acts like hydrochloric acid liberating bicarbonate and uniting with the sodium. The result is a lowering of the bicarbonate content of the serum. The blood may be obtained from an arm vein, or the external jugular. It may be collected in a syringe and then transferred to a tube under oil. We prefer to allow the blood to coagulate and to use the serum for the determination. The clot is thrown down by means of the centrifuge and the supernatant serum used for the determination.

The normal bicarbonate concentration of the serum of infants and children expressed as cubic centimeters of CO_2 gas, corrected to standard conditions, per 100 c.c of plasma, is found to vary between 50 and 70. When the bicarbonate concentration is less than 25 c.c. the patient usually has persistent and marked hyperpnea and is either in or on the verge of coma.

We have so far considered only such methods as aid in the diagnosis of acidosis and in the determination of its severity. Certain acids are now known to be capable of producing a severe degree of acidosis when present in the blood in sufficient concentration. Methods for the quantitative determinations of some of these acids in urine, and in such amounts of blood as may, with safety, be taken from children, have been described. With older children and adults a sample of urine can usually be readily obtained and tested for the presence of ketone acids, when these substances are suspected of being responsible for the condition. It is, however, often difficult with infants to obtain a sample of urine. Under such conditions the methods of Higgins and Hubbard for determining the concentration of acetone in the expired air are of value.

TREATMENT

In the treatment of acidosis we aim:

1. To relieve the hyperpnea.
2. To bring about the oxidation of preformed acids.
3. To check the overproduction of acid bodies.
4. To promote the elimination of non-oxidizable acids (phosphates, sulphates, chlorids, etc.).

5. To restore the bicarbonate to a safe level.
6. To correct the underlying condition whenever possible.
7. To restore the body fluids.

Certain measures have acquired a certain degree of popularity in the treatment of acidosis. These are:

1. The intravenous, intraperitoneal or subcutaneous administration of a 4 per cent glucose solution.
2. The administration by similar routes of normal salt solution or of a solution containing both salt and sugar.
3. The intravenous administration of a 4 per cent solution of sodium bicarbonate.

The utilization of these abnormal routes of administration is necessitated by the fact that children with acidosis vomit continually. With infants the veins may be very small or very difficult to locate. In either case the superior longitudinal sinus may be utilized by the experienced individual, but this is not without danger. The absorption of fluids injected subcutaneously may at times be very slow and the amount of fluid that may be administered in this way insufficient. These considerations have led, within recent years, to the use of the intraperitoneal route. The danger is very slight if one makes sure that the bladder is empty and precautions as regards asepsis are observed. The injection should be made in the midline a little below the umbilicus or to the right or left of the rectus abdominalis muscles, using a rather blunt, short-beveled needle. From 75 to 200 c.c. of fluid may be administered in this way at each injection. One should be guided by the amount of distention and the rapidity with which the fluid is absorbed. The injection may be repeated two or even three times daily if necessary. Solutions of sodium bicarbonate should never be injected either intraperitoneally or subcutaneously.

TREATMENT OF SPECIFIC CONDITIONS

Starvation.—This condition requires no treatment other than the administration of a properly balanced diet containing plenty of readily assimilable carbohydrate.

Recurrent Vomiting.—The indications for treatment are: (1) to administer carbohydrate in easily oxidizable form; and (2) to restore the body fluids with their normal content of bicarbonate.

In the majority of instances the administration of glucose by rectum or intravenously meets all of these indications. Glucose is easily and promptly oxidized. It in turn facilitates the oxidation of the ketone acids which bind the sodium of the blood and tissue fluids. The sodium then becomes free to unite with the ever-present carbonic acid and the sodium bicarbonate concentration is restored. With the glucose a considerable amount of water enters the body, which helps to restore, in part, the fluid which has been lost. It is, however, difficult to understand how it is possible for the organism to hold water as such after its glucose content has been oxidized unless some salt is administered with the water to give it the necessary osmotic pressure. Sugar is usually administered as a 4 per cent solution in water or normal saline. Large amounts must be given so that the child receives about 50 to 100 gm. of glucose in twenty-four hours.

The question of the use of alkali in non-diabetic ketosis as well as in other forms of acidosis has been much discussed. The experiments of Gamble and his collaborators show clearly that alkalis are not necessary for treatment of non-diabetic ketosis, due to starvation. One must not assume, however, that they are of no value in other forms of acidosis. Although the sodium concentration may be normal, the total amount of sodium bicarbonate within the body may be reduced. This is due chiefly to an actual loss of body water with its content of sodium bicarbonate. The majority of children will respond to the administration of glucose alone, but occasionally only the intravenous injection of 4 per cent sodium bicarbonate will relieve the hyperpnea and bring the child out of coma. Certainly the results which often follow the administration of bicarbonate to children with acidosis, complicating cyclic vomiting or acute diarrhea, are so striking as to leave no doubt regarding the beneficial effects of the treatment. When anuresis is present the administration of alkalis should be avoided. If given, an amount no greater than is sufficient to restore the bicarbonate to about two-thirds of its normal concentration should be injected. The method of calculating this amount will be given below. When the hyperpnea disappears, the child usually regains consciousness and the vomiting ceases. The amount of acetone and diacetic acid in the urine rapidly decreases. The oral administration of food may then be resumed. Cereals and milk should be administered and other articles of food rapidly added. Case 1 is the history of a patient with cyclic vomiting complicated by severe ketone body acidosis.

Case 1.—F. W. D., male, white, age 2½ years, weight 13 kg. *Diagnosis:* cyclic vomiting; acidosis (ketone bodies).

F. H.—Unimportant.

P. H.—Numerous digestive disturbances characterized by vomiting and often by fever and diarrhea. Attacks occurred at intervals of a few weeks to a few months. Lasted from 2 to 4 days. Last attack 6 months ago.

P. I.—Began suddenly November 20, 1922, with vomiting, which occurred several times during the morning and very frequently during the afternoon. Neither food nor water could be retained and the vomiting persisted when neither had been taken for some hours. Temperature on admission, November 21, was 100.2° F. Respirations 36.

P. E.—On admission child lay quietly in bed in a semistupor but could be aroused. Skin was dry, eyes sunken and respirations somewhat accelerated and very deep, suggesting acidosis rather than pneumonia. Lungs were clear on physical examination. The stupor became more marked so that the child was in deep coma and the hyperpnea was definite. On November 21 urine contained large amounts of acetone and diacetic acid. Four hundred and fifty c.c. of 5 per cent glucose was given intravenously and 300 c.c. of normal salt solution was injected into the peritoneal cavity. The next day the respirations were as labored as on admission and the child vomited once. Glucose given by rectum was promptly expelled. An additional 500 c.c. was given intravenously. This was followed by slight temporary improvement. Plasma bicarbonate 15 vol. per cent at 6 P. M. On November 22 175 c.c. of 4 per cent sodium bicarbonate was injected intravenously. The hyperpnea was definitely relieved. At 10 P. M. condition was very much better. Urine contained only traces of acetone and diacetic acid. Patient breathing quietly. Took fluid by mouth without vomiting.

On November 25 urine contained neither acetone nor diacetic acid. The child recovered completely.

Acidosis Associated with Acute Diarrhea, Dysentery, etc.—The indications in the treatment of this type of acidosis are: (1) to stop the diarrhea by proper feeding either with protein milk or buttermilk, and thereby to check the further loss of fluid; (2) to restore as quickly as possible the fluid loss by administering fluid by mouth or by subcutaneous or intravenous injection; (3) to restore renal function. Five per cent glucose solution or normal saline may be used. Seventy-five to 150 c.c. may be injected at one time and the dose repeated two or even three times daily. The administration of fluid dilutes the blood, restores the circulating blood volume, improves the circulation and often causes the kidneys to resume their acid-excreting function, thereby relieving the acidosis. Alkalis are usually unnecessary. If used they should be given as a 4 per cent solution of sodium bicarbonate made by weighing out the required amount of sodium bicarbonate in a sterile container and adding it to the proper amount of freshly distilled, cooled, boiled water. It need not be sterilized again after adding the bicarbonate. The management of children with this type of acidosis is illustrated by Cases 2 and 3.

Case 2.—J. D., age 6 weeks, colored, weight 3.2 kg. *Diagnosis:* severe diarrhea; acidosis.

F. H.—Negative.

P. H.—Not important.

P. I.—Began August 5 with diarrhea and vomiting. Had 10 to 12 loose, watery, green stools a day which contained no blood. Condition continued until day of admission, August 8, 1919. Temperature on admission 102.8°F.

P. E.—Well-developed and well-nourished colored boy. Somewhat drowsy. Marked hyperpnea. Respirations both costal and abdominal. *Urine:* contained albumin but no acetone bodies. Plasma bicarbonate 15 vol. per cent. The administration of 125 c.c. of 5 per cent glucose by intraperitoneal injection and 50 c.c. of 4 per cent sodium bicarbonate intravenously produced no improvement. After a total of 650 c.c. of 5 per cent glucose had been given intraperitoneally and 4 gm. of sodium bicarbonate by mouth, during a period of 48 hours, improvement began. An additional 850 c.c. of 5 per cent glucose was given in amounts varying between 130 and 170 c.c during the next 2 days and sodium bicarbonate was continued. Proper dietetic treatment checked the diarrhea and was followed by rapid recovery.

Case 3.—P. G. age 1 year, white, weight 6.7 kg. *Diagnosis:* severe diarrhea.

F. H.—Not important.

P. H.—Not important.

P. I.—Began October 20, 1920. Vomited once after night feeding. Had fever. Had 6 or 7 watery, yellow, slimy stools which did not contain blood. Admitted to the hospital October 22, 1920.

P. E.—An underdeveloped, undernourished white male child; appeared very ill; very drowsy; roused with difficulty, very shrill piercing cry. Fontanel depressed; eyes sunken, lips and tongue dry. Respirations slow but no hyperpnea. *Urine:* albumin 0, acetone +, microscopical 0. Five hundred c.c. of 5 per cent glucose was given intraperitoneally at 12:45 A. M. on October 23, 1920. Patient almost in coma. At 3:30 P. M. plasma bicarbonate was 30 vol. per cent. Seventy-five c.c. each of a 4 per cent sodium bicarbonate solution and a 5 per cent glucose solution was injected into the superior longitudinal sinus. Marked improvement followed. Plasma bicarbonate 70 vol. per cent, October 24; protein milk 1 ounce every 4 hours given and retained. Amount rapidly increased to 5 ounces at each feeding. Discharged November 19.

Acidosis Associated with Renal Insufficiency.—The treatment of acidosis occurring in children with renal insufficiency due to chronic organic disease is exceedingly unsatisfactory. Such patients are, as it were, balanced on a knife edge between acidosis and tetany. The administration of a small amount of hydrochloric acid for the relief of anorexia or the improvement of digestion will precipitate an attack of acidosis. On the other hand, the administration of sodium bicarbonate for the relief of the acidosis will precipitate an attack of tetany due to a lowering of the calcium concentration of the serum which even in untreated patients is low. When calcium chlorid is administered, the acidosis recurs. It is therefore important to control the administration of alkali either by determining the bicarbonate of the serum or by noting the first change in the reaction of the urine with dibromcresol (greenish yellow to purple).

One may calculate the amount of sodium bicarbonate that may be administered with reasonable safety. The normal bicarbonate concentration of plasma and of the other body fluids is about 0.3 per cent. In severe acidosis this is reduced to about 0.1 per cent or 1 gm. per 1,000 c.c. of body fluids. We may assume that about seven-tenths of the body weight is water; hence, if the child weighs 10 kg., the body will contain 7,000 gm. or 7 kg. of fluid. To restore the bicarbonate to the normal level, 14 gm. of sodium bicarbonate should be administered. However, with such patients this is dangerous and doubling the bicarbonate concentration will usually suffice. This will require 7 gm. of sodium bicarbonate or 175 c.c. of a 4 per cent sodium bicarbonate solution. Owing to the anatomical defect the results of treatment are usually unsatisfactory and the prognosis is invariably bad.

Case 4.—W. R., age 9 months, weight 4.8 kg.; born September 5, 1919; died June 19, 1920. *Diagnosis:* bilateral cystic kidney; acidosis; tetany.

F. H.—Unimportant.

P. H.—Birth history normal. Has had a variety of diets including woman's milk. On all of these he gained very slowly or not at all. Had diarrhea from time to time. At 4 months of age had influenza and pneumonia.

P. E.—Admitted to Harriet Lane Home, June 17, 1920. Temperature, 98°. A poorly nourished, poorly developed, anemic white boy. His muscular development was very poor. He was just able to hold his head up but could not sit up even with support. He had hyperpnea. The lower border of his spleen was felt 2 cm. below costal margin. *Urine:* albumin, trace; sugar, none; acetone, trace; no casts, no pus. June 18, plasma bicarbonate 20 vol. per cent. Calcium 7.4 mg. per 100 c.c. serum. Inorganic P. 12.5 mg. per 100 c.c. serum. Magnesium, 2.2 mg. per 100 c.c. serum. Alveolar CO_2 tension 15 mm. Hg. Sodium bicarbonate, 1.3 gm., was given every 4 hours. The next day the hyperpnea had disappeared but signs of tetany appeared. Child had carpopedal spasm and the Chvostek and Erb phenomena were positive. Sodium bicarbonate was discontinued. After 7 gm. of sodium bicarbonate had been administered the urine was still acid (normally child's urine becomes alkaline after 3 gm.). The plasma bicarbonate had increased to 46 vol. per cent. The calcium had decreased to 4.8 mg. Intravenous phthalein test showed 6 per cent excretion in 2½ hours. The child had the first convulsion at 2 P. M. on June 19 and a second one at 2:30 P. M. Blood-pressure, 118/76. He suddenly stopped breathing at 5:30 P. M. Respirations could not be restored.

PROGNOSIS

The prognosis of acidosis is always uncertain. In any case it must be looked upon as a grave complication. One hundred and forty-eight children with acidosis were treated at the Harriet Lane Home. In only 15 cases was the condition due to ketone acids. Five of these cases terminated fatally. Of the remaining 133 children, only 35 recovered. This is due, no doubt, to the fact that the majority of children were desperately ill when brought to the hospital. The bicarbonate concentration of the blood is not the sole criterion of the gravity of the patient's condition. Following the administration of sodium bicarbonate, the bicarbonate level may be restored to normal, the hyperpnea may disappear and yet the patient may die. On the other hand, even very severe cases of acidosis often respond favorably to treatment. The nutritional condition of the child at the time of onset is important. The prognosis of acute acidosis in well-nourished children is usually better than when the same condition occurs in those who are undernourished. The duration of the acidosis is a factor of considerable importance. In general the longer the condition has existed before treatment is begun, the worse the prognosis. Where the underlying cause is some irremediable anatomical defect or some metabolic disturbance not amenable to treatment, the prognosis is bad. Unless either of these conditions is present the results of treatment are often very striking, so that a child in profound coma with marked hyperpnea may regain consciousness within a few minutes after the injection of sugar solution or of bicarbonate is begun.

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CHAPTER XLV

ACIDOSIS WITH SPECIAL REFERENCE TO THE ACIDOSIS OF STARVATION AND CHRONIC DISEASE

WALTER W. PALMER

Introduction.—The term "acidosis" was introduced by Naunyn to designate the formation of beta-hydroxybutyric acid in metabolism and was generally used in clinical medicine in this restricted sense up to a decade ago. Naunyn's clear understanding of the results of this abnormality in the combustion of fats seems to be rather generally overlooked. In his textbook, *Der Diabetes Mellitus,* he writes [1]:

"In severe cases of diabetes—occurring especially in young people—there appears after a long duration of the disease an abnormal acid production. Since the acid or acids, the overproduction of which is important in diabetic acidosis, are excreted in the urine combined with alkali, and therefore withdraws alkali from the organism; in the case of copious and continued acid production (severe acidosis) there develops a deficiency of the alkali necessary for neutralization; this deficiency is shown by an increased excretion of NH_3."

Clearly, it was Naunyn's intention that the overproduction of a normal or abnormal acid should be designated as *acidosis,* and the effect of reducing the base of the blood below normal levels as *hypalkalität.* In view of the fact that at present the important types of acidosis result in a reduction of base, frequently called reduced "alkaline reserve," it is unfortunate that the term has been so universally disregarded in the literature, particularly English and American. As our knowledge of the physical chemistry of the acid base equilibrium and the regulation of this equilibrium has increased, together with the development of simple and accurate methods of clinical applicability for detecting abnormal changes in the normally slightly alkaline body fluids, the term acidosis has acquired a wide significance.

In 1877, Walter laid the experimental foundation of our knowledge of acid intoxication by feeding rabbits hydrochloric and other acids by stomach tube, and observing the physiological and chemical effects. When he gave hydrochloric acid in lethal amounts, there was an increasing hyperpnea and rapid pulse, ending in death, a picture resembling that described by Kussmaul in diabetic coma years before. The CO_2 content of the blood was much diminished by the administration of HCl, although the reaction of the blood always remained alkaline to the most sensitive litmus. Furthermore, he found that the simultaneous administration of sodium bicarbonate subcutaneously made it possible to increase the lethal dose of HCl threefold, and, when animals were apparently dead of acid poisoning, intravenous sodium bicarbonate would restore the pulse and breathing. He also observed that, as the result of HCl ingestion, the urine of rabbits, normally alkaline and free from ammonia, became acid and contained large amounts of ammonia. Increased amounts of ammonia had been found previously in severe diabetes, by Boussingault, and later confirmed by Hallevoorden.

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[1] Naunyn. Der Diabetes Mellitus, 2d ed., 334, 1906.

Six years after Walter's classical experiments, Stadelmann called attention to the fact that "the symptom complex of diabetic coma greatly resembles that of acid intoxication, as revealed by the work of Walter." This observation led Stadelmann to estimate the then known basic and acid radicals in the urine of a patient in diabetic coma. He discovered large amounts of an unknown acid. Quite logically, he believed this unknown acid to be organic and set about its identification. He isolated alpha-crotonic acid, which results when beta-hydroxybutyric acid is heated in acid solution. This error in technic was corrected a year later by Minkowski and Kulz. It was Stadelmann who first suggested the use of sodium bicarbonate in the treatment of diabetic acidosis. Magnus-Levy (1899) in a notable paper, showed that the chief source of beta-hydroxybutyric acid is the incomplete oxidation of the fat, and that death from diabetic coma may occasionally be prevented by the administration of large amounts of sodium bicarbonate.

Although acidosis as it occurs in diabetes mellitus was the chief form of acid intoxication recognized by clinicians for many years, it should be remembered that Kussmaul called attention to the similarity of the dyspnea in the terminal uremic coma of nephritis to that in diabetic coma. Jaksch brought forward chemical evidence of a reduced alkali content of the blood of nephritics with dyspnea by simple titration methods.

Since Lawrence J. Henderson's (1906-1911) exposition of the physiological importance of balanced solutions of phosphates and carbonates, and their rôle in the mechanism whereby the organism maintains a normal acid base equilibrium, there has been an extended interest in the theoretical and clinical consideration of the condition known as acidosis. As a result of numerous and exhaustive studies, chiefly by American, English and Danish investigators, our knowledge of the physicochemical properties of "buffer" solutions, of which blood and body fluids are the most important physiologically, has been greatly enhanced. Furthermore, through the clever methods for detecting acidosis, the presence of varying degrees of this condition has been discovered in a variety of diseases. However, it is safe to say that the most important form of acidosis is that which results from the faulty oxidation of fat, and occurs most frequently in diabetes mellitus and cyclic vomiting of children.

Definition.—Without apology, it may be stated that the blood is a "buffer solution of extremely complex composition.[2]

The constituents which take part in the buffer mechanism are plasma proteins, hemoglobin, bicarbonates, phosphates, carbonic acid, chlorids, free oxygen, urea and ammonium salts. Under normal conditions the concentration of these several factors varies within rather narrow limits and, what is still more important, the ratio of acid to basic reacting substances is extremely constant. It is the ratio of acid to base which determines the reaction (the hydrogen ion concentration) of the blood and body fluids. The bicarbonates outrank all other constituents of the blood in importance as buffers. When the concentration of the bicarbonates is reduced, the blood and body fluids are rendered much less efficient as buffer solutions, thereby increasing the tendency to the development of a disturbed acid-base ratio, for example, an increased hydrogen ion concentration.

For the present we may consider a condition of acidosis to exist *when there is a reduction of the bicarbonates of blood below the normal level, or when the ratio of acid to base is so altered that the hydrogen ion concentration of the blood is increased above the upper limits of normal range.*

Acid-Base Regulation.—Under average normal conditions of activity and food intake, the acid waste products of metabolism are in excess of the basic. Prompt elimination of these products is essential to life. The mechanism for dealing with this feature of human metabolism may be divided into two phases. The one provides for rendering the excess acid radical harmless, as soon as produced; the other furnishes a means for their elimination. In the first instance the contingency is met by the buffer quality of the blood and, to a limited extent, through the formation of neutral ammonium salt. Aside from the carbonates and phosphates in the plasma, there are the important buffer effects resulting from the interchange of HCL and H_2CO_3 between the hemoglobin and phosphates of the red blood-corpuscles. The elimination of acid products is effected largely through the lungs (CO_2) and the kidneys (non-volatile acids). The rôle of the bowel in the excretory process, though less well understood, is probably of minor importance. Fortunately the bulk of acid production is in the form of volatile carbon dioxid, which passes out through the lungs by simple physical diffusion. The kidney is able to rid the organism of the excess of acid radicals by excreting a urine more acid than blood and by utilizing ammonia to form neutral salts. Recent work indicates that it is in the kidney that ammonia may be taken from urea to be combined with acid radicals, thereby saving base for the body.

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[2] A buffer solution is one to which considerable amounts of acid or alkali may be added with a minimum change in the reaction (hydrogen ion concentration).

Diagnosis.—There are two types of acidosis which are of clinical interest, one in which the fixed alkalis, chiefly the bicarbonates, are reduced, and the other in which there is an alteration of the acid-base ratio with or without depletion of the bicarbonates. As may be surmised, the diagnosis must usually be determined by laboratory means, for in only the severest grades can the diagnosis be made clinically. A discussion of laboratory methods here is without the scope of this paper. The forms of acidosis of greatest clinical importance, at least in the present state of our knowledge of the subject, are those in which the bicarbonates of the blood are reduced below the normal, and can best be determined by the direct method devised by Van Slyke and now in general clinical use. Alteration of the acid-base ratio in the blood involves a determination of the hydrogen ion concentration (pH) of the blood, either by direct or indirect means. Under proper precautions, the colorimetric method of Cullen and Van Slyke promises to be the most useful, because of its accuracy and simplicity.

For a discussion of the acid-base equilibrium and its regulation within the organism, the reader is referred to the comprehensive articles of L. J. Henderson, Van Slyke, and Evans.

Treatment and Conditions in Which Acidosis Occurs.—That acidosis is an abnormal physiological state, which may appear in a variety of pathological conditions, and *not a disease* should be clearly appreciated. Any abnormal process which leads to a production of acid radicals more rapidly than they may be discarded or injures the eliminative mechanism may result in acidosis. With the development of suitable clinical methods for determining directly the bicarbonate concentration in the blood, acidosis has been found in a large number of diseases formerly not suspected. Of first importance are the conditions which lead to the production of large amounts of beta-hydroxybutyric acid, that is, diabetes, cyclic vomiting of children, starvation and malnutrition of whatever cause, occasionally infectious diseases and anesthesias (chloroform and ether). Varying degrees of reduction of the blood bicarbonates (commonly spoken of as alkaline reserve) have been found in renal disease (uremia, acute nephritis, chronic nephritis with hypertension, pyelonephritis), cirrhosis of the liver, diarrheal diseases of children, acute infections, in which no notable amount of beta-hydroxybutyric acid is produced (Asiatic cholera, bacillary dysenteries, rheumatic fever, pneumonia, Weil's disease, etc.), poisonings from chemicals (salicylates, methyl alcohol), wasting diseases (cancer, pernicious anemia, etc.), severe burns, traumatic shock, etc.

Conditions in which the acid-base ratio is altered, leading to an increase in the hydrogen ion concentration of the blood, may be found in any of the diseases with a reduced bicarbonate level, and, in addition, in those without a lowered alkaline reserve, such as pneumonia, asthma, cardiac failure, severe anemias and carbon monoxid poisoning. It is fair to say, however, that in carbon monoxid poisoning, there is frequently an associated lowered bicarbonate concentration. Concerning the treatment of acidosis, the discussion will be limited to non-diabetic conditions in adults. The treatment of acidosis in diabetes mellitus and in children will receive special attention in their appropriate chapters.

General Measures.—Of great importance is the treatment of the disease process underlying the acidosis. A safe point of view is to consider the acidosis as a "symptom" from which the patient needs prompt relief, while measures in the conduct of the case should be directed to prevent any recurrence of the condition. Where acidosis is due to the production of large amounts of ketone bodies (beta-hydroxybutyric acid, diacetic acid and acetone) the immediate fundamental fault is in the oxidation of fat, either from the lack of sufficient glucose properly to burn the fatty acids completely, or because the body cannot utilize glucose. As diabetes is the disease par excellence where there is an inability to burn glucose, and is to be specially considered under this head, it only remains to call attention to the fact that, in those conditions where there is insufficient glucose properly to oxidize the fat, more should be supplied by mouth, rectum, subcutaneously, or intravenously. In adults, starvation, from whatever cause, is the one important condition which may need special measures directed to the increasing of the glucose intake.

Less is known about the acidosis which may result from the production of abnormally large amounts of acids other than beta-hydroxybutyric acid. In methyl alcohol poisoning, the offending acid is formic acid, the oxidation product of methyl alcohol. An increased excretion of organic acid has been observed in very ill cases of pneumonia, although there is seldom found any profound reduction of the alkaline reserve.

Impairment of the renal function, if severe, may lead to a high-grade acidosis, due to a retention of acids, phosphoric chiefly. Modification of diet is clearly indicated, and will be discussed in the chapter devoted to the treatment of nephritis.

Acidosis, due merely to an altered acid-base ratio, without reduction in bicarbonate, is best treated through care for the underlying condition. In respiratory difficulties, where this situation is most frequently encountered, the use of oxygen to facilitate gaseous exchange is of value.

Yandell Henderson and his associates, on the grounds that the acidosis accompanying traumatic shock and anesthesia (ether and chloroform) may be the result of hyperpnea, have advised the inhalation of an atmosphere rich in CO_2. Clinically, the evidence seems to favor bicarbonate administration. It is clear from the contradictory results that more clinical and experimental facts must be brought forward before settlement of the question is possible. The author has had no personal experience in the treatment of either condition.

When Should We Treat Acidosis Per Se?—The effect of mild grades of acidosis over long periods is unknown. By mild grades we mean a reduction of the blood CO_2, 10 to 15 volumes below the lower normal level of 55 volumes per cent. Until information contra-indicating such a procedure appears, it would seem wise and rational to restore the bicarbonate in the blood to a normal level by small doses of sodium bicarbonate. Clinical manifestations, such as headache, weakness, nausea and dyspnea, are most likely to appear when the blood CO_2 is about 30 volumes per cent or below. Occasionally the above symptoms occur with a blood CO_2 of 35 volumes per cent, but in the experience of the author this is unusual. Certainly, in situations where the base of the body is diminished sufficiently to produce symptoms, active measures to supply the deficit would seem indicated. The medical profession is not unanimous in advising the administration of sodium bicarbonate in severe diabetic acidosis. Indeed it is true that with careful treatment this may not be necessary in many cases, for with proper dieting the production of the ketone bodies is reduced, and the base combined with the ketone acids is liberated through oxidation of these acids and utilized in reforming bicarbonate in the presence of an ample supply of CO_2. The same consideration holds for other conditions in which the ketone acids are responsible for the development of the existing acidosis. However, when properly administered, the author has never seen any injurious effects from the use of sodium bicarbonate in combating acidosis from any cause whatsoever. Although it is true that treatment of the underlying condition will in most instances correct the error in the acid-base balance, it is a rational and justifiable procedure to make the patient more comfortable. With the above facts in mind, we may now consider special measures in the treatment of acidosis.

Special Measures.—In the treatment of acidosis, two measures of prime importance are the introduction of liberal amounts of fluid and alkali administration to restore the blood bicarbonate to a normal level.

Fluids.—Large quantities of fluids aid in the elimination of the deleterious acid radicals, and, in the more severe grades of acidosis, replenish the blood. It is not infrequent to observe a hemoglobin of 150 per cent in severe diabetic acidosis, and a return to 100 per cent after six or eight hours of an abundant fluid intake. It should be remembered that the kidney will not excrete beta-hydroxybutyric acid in a concentration much in excess of 1 per cent. While formerly in cases of severe diabetic acidosis a daily excretion of as much as 100 gm. of ketone bodies in the urine has been occasionally observed, the author has never encountered an excretion of half this magnitude. The value of a liberal fluid intake is equally great in abnormal acid production other than the ketone acids, and where the acidosis is due to the inability of the kidney to excrete rapidly the acid radicals. In renal disease, the above considerations hold, for the difficulty is the lack of the power of concentration of the acid substance on the part of the kidney. A fluid intake of 5 liters the first day, and 3 to 4 liters thereafter, is adequate.

The nature of the fluid and manner of administration is of some importance. When it be proper to give fluids by mouth, and there is no contra-indication to the use of sugar, sweetened drinks flavored with fruit juices are sometimes preferred by the patient to plain water. Alkaline waters, either charged or uncharged with CO_2, are occasionally well taken. It may not be out of place to call attention to the fact that severe acidosis may be associated with nausea, and very large amounts of fluid by mouth may increase the nausea and induce vomiting. The author believes it is a mistake to give very cold water, and, when the patient will take warm fluid, the latter is preferable. Two hundred c.c. every hour is about the maximum that can usually be given by mouth. Should supplementary fluids be necessary, 0.9 per cent saline may be given per rectum, by the Murphy drip method, or by giving 200 c.c. by rectal tube every four hours. A certain number of individuals do not take fluids by the rectal route well, and the next method of choice is by hyperdermoclysis. This is frequently painful and strenuously objected to on the part of the patient. In any case, the author believes it inadvisable to give more than 500 c.c. of saline solution under each breast in twenty-four hours. The remaining method which may be used as a last resort is the intravenous administration of saline solution or, if glucose is indicated in treatment of the underlying condition, 5 per cent glucose solution. The precautions to be observed are to give not over 800 c.c. at a time, and then very slowly, taking at least one-half hour for the introduction of the fluid. With care in the modern technic of intravenous therapy, infusions may be given frequently with safety. The author has never had occasion to combat acidosis in diseases of which edema is a prominent feature. Should edema be present, the giving of large amounts of fluid would seem to be unwise.

Normal saline or 5 per cent glucose solution in 500 to 1,000 c.c. amounts may be given intraperitoneally. This route is especially convenient in infants or individuals where fluid by vein is desirable but difficult.

The lower bowel should be emptied either by saline catharsis or enemata.

Alkali Administration.—Within recent years, some writers, notably Joslin, have urged against the use of alkali (sodium bicarbonate) in the treatment of diabetic acidosis. The argument advanced by its opponents in diabetes is brought forward for any acidosis due to the overproduction of the ketone bodies. It is quite true that, as soon as proper oxidation of the fatty acids is restored, the base held by the ketone acids is made available for the formation of bicarbonate and the normal bicarbonate level tends to be restored. It is held that an increase in the excretion of the ketone bodies follows the administration of sodium bicarbonate, implying, if not actually stating, that the giving of this drug leads to an increased production of beta-oxybutyric acid. Nothing could be more unwarranted. It would be equally reasonable to explain the increased excretion of ketone bodies on the basis that the increase in blood bicarbonate facilitates excretion, thereby freeing the body of these undesirable acids. It is true and important, however, that the unintelligent administration of large amounts of sodium bicarbonate may be productive of harm. In the experience of the writer, both on hypothetical and practical grounds, it is reasonable, rational, and in many instances highly desirable to restore the bicarbonate to its normal level through alkali administration. I may again call attention to the fact emphasized earlier in the chapter that the treatment of the condition underlying the development of acidosis is of primary importance.

Only sufficient alkali should be given to bring the level of the bicarbonate in the blood back to normal. When this point is reached, all that can be expected from the use of sodium bicarbonate has been gained in the combating of acidosis. Therefore, some adequate control of the amount necessary to accomplish this purpose is essential. The most satisfactory and reliable method is the direct estimation of the bicarbonate content of the blood devised by Van Slyke. When this method of control is available, the amount of sodium bicarbonate required to restore the blood bicarbonate to the normal level may be estimated by the formula of Palmer and Van Slyke.

$$\text{Gm. } NaHCO_3 = (60 - \text{plasma } CO_2) \times \frac{\text{weight in kg.}}{38},$$ the plasma CO_2 being expressed in terms of volumes per cent.[3]

Should the means of determining the plasma CO_2 not be available, observation of the reaction of the urine is of considerable service, provided there be no infection of the urinary tract with bacteria, the activity of which makes the urine alkaline. In no instance should sodium bicarbonate be given after the urine becomes alkaline or neutral to litmus. Where there is injury to the function of the kidney, as it applies to the regulation of the acid-base equilibrium, particularly in renal disease, the control of the reaction of the urine by litmus is inadequate. In diabetes mellitus, the function of the kidney is frequently impaired, thereby rendering litmus an unsafe indicator. In these cases it is imperative to stop the administration of sodium bicarbonate as soon as the first distinct effect on the reaction of the urine is observed by some suitable indicator. For this purpose a 2 per cent watery solution of sodium alizarin sulphonate may be used as follows: Before initiating the alkali therapy, secure a fresh specimen of urine, to 1 c.c. of which 25 c.c. of water are added. After dilution with water, add 2 drops of the indicator, and save as a standard. After each dose of soda, test the urine in a similar manner. When there is a distinct change toward the red to reddish purple, the desired effect has been obtained. Other indicators may be used, such as methyl red for the more acid urines, bromcresol purple for reactions nearer neutrality. The reader should consult the original articles quoted in the list of references for details in the technic of hydrogen ion concentration estimation in the urine.

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[3] The formula is derived as follows: 1 gm. of $NaHCO_3$ contains 267 c.c. of CO_2 measured at 0°, 760 mm. If the body fluids are estimated at 700 c.c. for each kg. of body weight, then the distribution of 1 gm. of bicarbonate among them would raise the CO_2 content, in c.c. per 100 c.c. of fluid, by $\frac{267}{7W} = \frac{38}{W}$ c.c., W representing the body weight in kg. Conversely, the amount of bicarbonate necessary to raise the CO_2 by b volumes per cent would be $\frac{bW}{38}$. If $b = 60 -$ plasma CO_2, the amount by which the bicarbonate CO_2 in the plasma has fallen below 60 volumes per cent, then the bicarbonate required to raise it back to 60 would be $\frac{W}{38} \times (60 - \text{plasma } CO_2)$. Palmer and Van Slyke, and Palmer, Salvesen and Jackson have shown this equation to be sufficiently accurate for practical purposes.

The dangers of increased bicarbonate concentration in the blood have frequently been pointed out, for tetany may accompany such a state. It is probably true that death has been hastened by the ill-advised and uncontrolled administration of sodium bicarbonate in patients suffering from nephritis. Furthermore, if alkali is given to normal individuals in amounts sufficient to depress the reaction of the urine much below neutrality, a pH of 8.5, albuminuria may result. Also, large doses of sodium bicarbonate may cause diarrhea.

Methods of Administration.—As in all therapeutic procedures, the method of choice is by mouth. In severe acidosis in diabetes, with unmistakable symptoms of impending coma, drowsiness, hyperpnea, and a plasma CO_2 below 25 volumes per cent, the time element is a factor and intravenous administration supplemented by oral and rectal measures is desirable.

Oral Administration.—It is unwise to attempt this method of administration if there be nausea, or if the bicarbonate produces nausea. On the other hand, the writer has seen individuals with severe diabetic acidosis, in which nausea has been relieved by the ingestion of sodium bicarbonate, and, furthermore, there has been a craving for the drug so long as a lowered plasma bicarbonate pertained. Sodium bicarbonate by mouth should never be given in amounts greater than from 3 to 5 gm. per hour, diluted in 150 to 200 c.c. of water, and never persisted in after the development of any untoward gastric symptoms, always remembering that after the desired effect has been secured [4] the drug should be discontinued.

Rectal Administration.—Sodium bicarbonate may be given by rectum in a 4 per cent solution by Murphy drip, or in 200 c.c. amounts every four hours. Certain subjects do not tolerate bicarbonate solution by rectum, and this method has to be abandoned.

Intravenous Administration.—Sodium bicarbonate solutions for intravenous use should be made with normal saline, and sterilized by boiling ten minutes, or autoclaved at 20 pounds pressure for fifteen minutes. This procedure converts some of the bicarbonate into carbonate, and formerly sterile CO_2 was bubbled through the solution to insure a pure bicarbonate solution. In our experience this is not necessary. The precaution to be observed is a slow administration, as in any intravenous infusion, otherwise a chill may be produced. The author prefers a 5 per cent solution and never under any circumstances introduces more than 500 c.c., which is given over a period of at least one-half hour. Large amounts of bicarbonate solution introduced into the vein rapidly not infrequently result in sudden death. Eight instances of sudden death, after 1 liter of 2 per cent solution by vein, quickly given, are known personally to the writer. On the other hand, when given as directed above, no untoward effects have ever been observed. It is preferable to give 250 c.c. of a 5 per cent sodium bicarbonate solution every four hours, until the desired effect has been obtained.

Sodium bicarbonate solution with the pH properly adjusted to 7.4 may be given in hypodermoclysis. This procedure is never used, nor is it approved by the author.

In view of the several absurdly unintelligent and unjustifiable uses of sodium bicarbonate in the past, I am constrained to repeat again that after the plasma CO_2 has been restored to its normal level, the administration of the drug should be discontinued.

The treatment of acidosis as it occurs in specific diseases must necessarily be discussed in their appropriate chapters. The attempt has been made to outline only general principles underlying the treatment of acidosis in general.

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CHAPTER XLVI

THE TOXEMIAS OF PREGNANCY

A. N. Creadick

Pregnancy should be, and in the majority of cases is, a physiological process. However, the border line between health and disease in this condition is vague, slight modifications serving to convert a normal physiological process into a pathological condition. The agents which induce this change from normal to abnormal may be associated with the pregnancy itself or may be accidental and bear no relation to the pregnancy. The latter group includes the acute and chronic constitutional infections, while the former group, the diseases peculiar to pregnancy, are collectively spoken of as the toxemias of pregnancy. These may manifest themselves clinically by excessive vomiting, convulsions, skin lesions, or other evidence of general disease. In these diseases peculiar to pregnancy, slight deviations from the normal metabolism frequently give rise to evidences of auto-intoxication, which range from mild manifestations, speedily relieved, to a severe toxic condition which terminates fatally. Between these extremes all gradations occur. The toxemias are related, in that pregnancy is essential to their occurrence, and that the fault lies in the metabolic processes.

The metabolism of the mother is profoundly affected by pregnancy, as is evidenced by the storing of nitrogen, of fluids, of calcium salts and the adding of fat. The elimination of fetal waste products as well as maternal waste products throws a heavier burden on the excretory functions, skin, bowel and kidney. It is a question whether the metabolic abnormalities result from irregularity in the digestion and absorption of foodstuffs on the part of the mother or whether they are due to a liberation of fetal waste products, or, in the third place, to the inability of the maternal eliminatory organs to excrete normal maternal and fetal waste products. Such distinctions may distinguish the types of toxemia, and the field is at present an attractive one for investigation. Further confusion arises from the fact that totally different pathological conditions produce identical clinical symptoms, such as fever, albuminuria, convulsions, or coma. At the moment our classification of these toxemias must rest on histological and pathological findings and not on clinical phenomena. The time may come, however, when a specific toxic agent will be isolated from the maternal blood in vivo.

It was formerly supposed, and is still occasionally argued, that all of these toxemias have the same fundament. Only lately Fitzgibbon remarked that the several toxemias had a common etiological basis because they had one common symptom, namely albuminuria, and the other symptoms, whether they were hemorrhage, convulsions or pernicious vomiting, were incidental. On the other hand, we understand that widely different pathological lesions may be associated with similar symptoms. That such dissimilar pathological findings can have a common etiology is at present an untenable hypothesis. Ewing considered acute yellow atrophy and eclampsia as manifestations of the same toxemia. It is true that acute yellow atrophy and eclampsia cannot be distinguished clinically if the patient is first seen in coma, and that during convulsions in the last trimester of gestation one cannot specify whether such attacks are of nephritic or eclamptic origin. Nevertheless, careful inquiry into the prodromal signs and symptoms or, later, autopsy findings can differentiate the several conditions. In view of the differences in clinical picture, blood chemistry, urine analysis and pathological histology, each type of toxemia should be regarded as an entity until the etiological factors are known.

Therefore, we subdivide the toxemias into: (1) pernicious vomiting; (2) acute yellow atrophy of the liver; (3) nephritic toxemia; (4) impending eclampsia; and (5) eclampsia.

PERNICIOUS VOMITING

Etiology.—Beginning in the sixth or eighth week of pregnancy, more than half of all pregnant women complain of nausea and occasionally of vomiting upon arising in the morning; whence the term "morning sickness." While the condition usually subsides in from six to eight weeks, vomiting may last for a longer period, occur at more frequent intervals and, exceptionally, persist throughout the whole period of gestation. The milder picture has probably been observed from time immemorial and is so frequent that it is regarded by the laity, and by many physicians, as physiological. Certainly in the earliest descriptions, and even as late as 1718, the authors who mention the condition apparently do not regard it as fatal. Rigby, in 1841, stated that "a sick pregnancy is a safe one," thereby expressing what was probably regarded by the profession in the previous century as a truism. But in 1852 a discussion concerning the justification for therapeutic abortion for the relief of severe cases of vomiting took place before the Academy of Medicine in Paris, thus proving that, in France, at least, the disease had evidenced itself in a grave form.

Since that time the mass of literature on the subject gives further proof that incoercible or persistent vomiting has increased in incidence and in severity, especially in France, England and the United States. Horwitz called attention to the variation in incidence in different countries. The more severe picture is less frequent in Germany and Russia, where several authors (Hohl and Frank) have stated that they never have seen a case of vomiting of pregnancy end fatally. On the other hand, every general practitioner in the United States doubtless can furnish several instances from his records of extremely grave types of this disease. This condition, in which vomiting may persist until neither food nor water can be retained, is grave, is spoken of as hyperemesis gravidarum or pernicious vomiting, and sometimes leads to fatal termination.

Reflex Vomiting.—While there is probably a toxemic etiology behind the simplest forms of vomiting of pregnancy, apparently unrelated external influences frequently excite the condition. Of these factors, the psychic elements are the most frequent, while, on the other hand, reflex irritation may occur. The exciting cause in the so-called reflex variety is some anatomical abnormality elsewhere in the body, but particularly in the generative tract. Thus, retroflexion of the uterus, ovarian cyst, and other causes of that nature have been blamed. Grailey Hewitt is commonly regarded as the original exponent of the theory that uterine displacements play an etiological rôle in persistent vomiting, but the idea was advanced by Busch and Moser twenty-eight years before Hewitt's first monograph appeared. It is doubtful if anteflexion is a factor, as Hewitt suggested, but retroversion and incarceration undoubtedly favor the occurrence of vomiting. Incarceration, hydramnios and certain cases of multiple pregnancy lead also to an abnormal thinning of the uterine wall, which Dance suggested as the etiology rather than a coincidence of vomiting. Horwitz, Tuszkai and Martin demonstrated a coincident myometritis and irritation of the adjacent peritoneum. Inflammatory changes in the cervix and endometrium have been associated with fatal toxic vomiting and such lesions have found an exponent and followers who claim an etiological specificity for each finding. The very multiplicity of these lesions and the obvious psychic effect of such therapy as manual reposition, or dilatation of the cervix without other procedures, makes one skeptical of the specificity of any one condition. This leads one to believe that too keen attention was devoted to the generative tract, to the exclusion of the findings elsewhere in the body. The association of hydramnios and multiple pregnancy with pernicious vomiting may more likely be due to an excess of the toxic agent rather than to the overdistention of the uterus, while the frequent occurrence of the symptoms with hydatidiform mole is doubly interesting. In the first place, the fetus itself is not essential for the production of pernicious vomiting; and, secondly, there is a distinct increase in the trophoblastic elements in hydatidiform mole formation to which has been ascribed a toxic etiological significance. Occasionally vomiting may be aggravated by the presence of a tumor arising from the adnexa and distorting the pelvic organs. Krassowsky's and one of Williams' cases bear out this point. While the reposition of the uterus, or the removal of the tumor, as the case may be, may be followed by immediate relief, less emphasis is being placed nowadays upon the reflex cause of vomiting, in view of the fact that such conditions can scarcely influence the etiological agent, and that the treatment has a psychic effect rather than a specific therapeutic action.

Psychoneurotic Vomiting.—There is a functional unbalance in the higher mental processes that accompanies pregnancy. This fact has long been recognized and many authors speak of vomiting as of hysterical origin. Kaltenbach evolved a theory to explain the very large group of these cases in which there was no lesion to provide reflex irritation and also called attention to the sparse and inconstant pathological findings. He concluded that the majority of women who complained of persistent vomiting were suffering from a neurosis which was not apparent until the pregnancy supervened. He called attention to the fact that if such cases were properly treated the need for therapeutic abortion would be reduced to a minimum. In a monograph published in 1906, Williams proposed that the term "neurotic vomiting" be applied to this group of cases, and said, "to any one who has had considerable experience with this class of cases there can be no doubt that in many the vomiting must be attributed to some neurotic condition, as is manifested by the remarkable cures which sometimes follow all sorts of unphysiological procedures, as well as the mere threat to induce abortion, or a feigned attempt to bring it about. It is more than probable that the vast majority of cures following the application of leeches to the epigastrium or cervix, the dilatation of the latter by Copeman's maneuver, or the application of various drugs, are susceptible of a similar explanation." This viewpoint has not escaped criticism; for example, in discussing Graefe's first paper in support of the psychic element in vomiting of pregnancy, Winscheid said that the theory was extreme and did not explain the emaciation and cachexia which was present in severe cases. However, severe prostration from inanition and starvation has been observed, and apparently has been relieved by an appeal to the patient's mind alone. Thus, but lately, a private patient of mine, of intelligence and education, suffered from a severe type of vomiting while in the second and third months of her third pregnancy. There had occurred a marked loss of body weight, while no food and but little fluid could be retained. She responded promptly to appropriate treatment. After the pregnancy had progressed satisfactorily, we were in conversation over the previous difficulties, when she surprised me by discussing the matter very frankly. She explained that there had been no intention to vomit, but that there had existed a complete abandonment of her inhibitions, so that she could not "will herself against vomiting."

The more frequent appearance of excessive vomiting in illegitimate pregnancies, in the recently widowed and in an environment of marital or financial distress lends strength to Kaltenbach's theory. It is well known that there is usually pronounced aversion to this particular pregnancy, not that the patient is not willing to have a child, but that, owing to some social condition surrounding her at the moment, pregnancy, or this particular pregnancy, is not a welcome gift. Cures following induction of general anesthesia, without any operative procedure, the use of hypodermic injections of sterile water and similar methods of therapy point to the suggestive character of treatment. The use of the term "neurotic" is unfortunate, not by reason of its inaccuracy, but by reason of the implied triviality of the condition so labeled in the minds of the medical practitioner. As a matter of fact, the psychologists use the term "psychoneurosis" for such conditions, implying a functional disorder which may arouse a latent pathology.

Undue emphasis should not be placed on this type of vomiting, nor on the psychoneurotic element contained in it, for the border line between the psychoneurotic type and the severer, or truly overwhelming toxemia, is very vague. These patients sometimes progress, if untreated, into a critical state, from which no method of therapy will avail in repairing the damage that has been done. Original investigation must be directed toward securing some determining factor that will differentiate a psychosis from a profound toxemia.

Toxemic Vomiting.—Evidence of the toxemic origin of vomiting in pregnancy is based tentatively on the appearance of icterus, albuminuria, hemoglobinuria, ketonuria, occasional instances of peripheral neuritis, coffee-ground vomitus, coma and death. Each of these symptoms, however, could be called into question and ascribed to some incidental concomitant of pregnancy. Just so have the hepatic lesions, regarded by Williams and Stone as specific evidence of toxemia, been questioned largely by biochemists on the ground that liver lesions have not been demonstrated which parallel the severity of the disease, which could be quantitated by functional tests, and which could be claimed as specific for the disease. The four main theories as regards the possible sources of the toxemia respectively indict: (1) the gastro-intestinal tract; (2) ovarian dysfunction; (3) the ovum and its implantation products; and (4) liver insufficiency.

Exponents of the theory of auto-intoxication due to disorders of the gastro-intestinal tract base their claim on the presence of indol and skatol in the urine of women suffering from vomiting and in whom pregnancy also exists. Dirmoser, in 1901, was the most ardent advocate of this theory, and based his opinion upon instances similar to the case of Fischl, where the patient suffering from torpor, hyperpyrexia, and severe continuous vomiting was relieved by the evacuation of a fecal impaction. Eulenberg collected a list of cases of neuritis associated with pregnancy and vomiting and presented them as irrefutable proof of the fact that the condition was toxic in origin. The successful employment of forcing large quantities of fluid in the cure of the condition suggested some intestinal cause. It is an equally tenable hypothesis that the results are attained by the elimination of toxins derived from another source and not solely to the relief of an intestinal toxemia.

The theory in regard to the ovarian origin of vomiting of pregnancy comes from Pierrehughes, whose views were presented in 1902. His suggestion is that vomiting of pregnancy may be due to a perverted corpus luteum secretion, or to an absence of sufficient corpus luteum secretion. Unfortunately his argument can apply, not only to the ovary, but to any other of the glands of internal secretion, as well as to the liver. There is no specific proof that the ovary is the sole source of the toxemia except in those instances of patients who recovered following the administration of ovarian extract. Turenne, Chirié and Perrot, and lately Hirst (J. C.) have revived and reasserted their belief in this etiology. Curiously, equally eminent German clinicians are now recommending extirpation of the corpus luteum to cure the toxemia.

In placing the blame on the fetus or the trophoblast, the name of Veit is inseparable from the theory. In 1902 he claimed that the fetal products gaining access to the maternal channels ordinarily were rendered harmless, but that in excessive amounts the protective mechanism was overcome and certain so-called syncytiotoxins were developed which produced vomiting. Veit injected into experimental animals various quantities of an emulsion of human placenta, and, upon finding a reaction and changes in the kidney and the presence of albumin in the urine of those animals, thought he had proved his point. Naturally, the syncytiotoxin theory assumes an important place in the discussion of the disease. However, we now realize that Veit produced a protein intoxication and an improperly controlled experimental proof. I have called attention to the fact that the fetus itself is not necessary to the production of toxemia of early pregnancy, for vomiting may occur in conjunction with hydatidiform mole, in which death and the absorption of the fetus has occurred. I also said that this condition showed an overgrowth of the trophoblast. There is a resistance on the part of the decidua of the uterus to the tryptic ferment in the trophoblast of the ovum. This struggle between the fetal invasion and the maternal tissues produces an area of marked degeneration, necrosis and fibrin formation. Such a zone of cell death by enzyme action must flood the maternal circulation, and may embarrass the organs of elimination at just the period when the early toxemia usually appears. Whether this flood of waste products overtaxes the metabolism of the mother, or whether it overtaxes the eliminatory organs, is open to discussion, but my interest is aroused by the hypothesis that the primary etiological factor lies in the product of conception itself, and that the subsequent evidence may lie in the liver or kidney.

The responsibility of the liver for the toxemia is an idea which was advanced in the latter part of the nineteenth century. Pinard is the exponent of the hepatotoxemic theory, and his pupil, Bouffe de St. Blaise, is the first to record autopsy findings which conform to this theory. The autopsy by Lindemann also confirms this view. In 1903, Stone observed a number of cases in which the liver presented a lesion usually attributed to acute yellow atrophy; the entire central portion of each lobule had undergone necrosis, while the peripheral portions showed signs of fatty degeneration—only a few liver cells remaining normal. Following this, Ewing presented the autopsy records of 4 cases dying from vomiting of pregnancy, 1 of whom had a convulsion immediately before death. From his observation on these cases, Ewing believes that all toxemias of pregnancy are of the same origin, and that the liver lesions are their specific histological evidence. After the appearance of Opie's article on Zonal Necroses of the Liver, Williams, in his monograph (1906), cited 4 cases which came to autopsy in his clinic, and the latter author stated that the lesions of pernicious vomiting and of eclampsia attack the liver in different zones and present a different histological picture; therefore, that their fundamental etiology is of a different source.

Pathology.—From that time the anatomical findings in fatal cases have rested on the lesions demonstrated in the liver and kidney. The liver lesion described by Stone, Ewing and Williams, confirmed by Winter and Hofbauer as specific for this condition, consists of a central necrosis of the liver lobule, together with marked deposition of fat, "so great in extent that, upon staining fresh sections with sudan red, practically the entire specimen seems to consist of fat." The renal lesion consists of a cloudy swelling confined to the convoluted tubules, which are filled with a granular débris. These lesions usually appear in the terminal stages of the condition. Whether the liver lesion precedes the renal lesion, or vice versa, there is at present some argument. Both lesions have been ascribed to starvation and to inanition of the patient. The similarity of the pathological picture with that seen in chronic chloroform poisoning has been pointed out, but many of these cases have received no chloroform, and the lesion has appeared in spite of operative interference.

Differential Diagnosis.—Ordinarily acute yellow atrophy appears in the latter half of pregnancy, while pernicious vomiting is usually a disease of the first trimester. If a similar etiological factor is ultimately demonstrated in acute yellow atrophy and pernicious vomiting, it will be difficult to explain the variations in the clinical course and anatomical findings. While the specificity of liver necroses has been questioned in these manifestations of toxemia, namely, pernicious vomiting, acute yellow atrophy and eclampsia, there is abundant evidence that the liver function is easily disturbed in all of them. In this connection it is interesting to note the incidence of epidemics of catarrhal jaundice and icterus gravis with their peculiar fatality in pregnant women. The glycogen-storing function of the liver is impaired in pregnancy, according to Payer, although Charrin demonstrated an unusual storage of glycogen in the liver. Titus recently claimed to relieve the toxemia and prevent the liver necroses by the injection of glucose solution intravenously. The last-mentioned author, while not always able to save the patient suffering from the grave types of toxemia, was unable to demonstrate at autopsy the liver necroses in cases which had received glucose injections. Underhill and Rand gave dextrose solution by bowel, in order to combat the starvation. While the majority of the patients improved, one case so treated showed an increase in the toxemia. Falk and Hesky claim a parallel between the glycogenic function of the liver and the "ureagenic" function, while Legneux found that sugar tolerance was impaired in pernicious vomiting. The latter author gave a grave prognosis when the patient could not assimilate 1 gm. of cane sugar per kg. of body weight. Alimentary glycosuria or intravenous ingestion of glucose, therefore, may prove useful clinical tests for hepatic insufficiency.

The cases reported by Williams demonstrated an alteration in the relative amounts of nitrogenous products in the urine, particularly a rise in ammonia. When the ammonia output was measured in ratio to the total nitrogen, the factor obtained was given the name "ammonia coefficient." Williams stated that when this ratio was 3 to 5 per cent there was no serious metabolic disturbance, and the vomiting was neurotic in origin. On the other hand, when the coefficient rose to 20 or 30 per cent, even 47 per cent in one instance, a toxemia was present, and the condition grave. It was admitted that this high ammonia output occurred in other conditions, for instance, acute yellow atrophy and phosphorus poisoning (Neuberg and Richter), acute gastro-enteritis in children (Czerny and Keller), marked constipation (Glaessner), and such conditions as high fat ingestion (Schittenhelm), especially with a high fat content in the blood (Pfaundler). In these latter conditions, the high ammonia output may be an expression of an acidemia. In view of the recent microchemical analyses of Folin, and the hypothesis of Nash and Benedict, the ammonia output is less likely to be a measure of liver efficiency, but rather points to a change in renal metabolism. Underhill and Rand found a high ammonia coefficient in cases of vomiting of pregnancy, which they attributed to the starvation, rather than to a toxemia. Gilliat and Kenneway concurred with Underhill and Rand, and suggested that the appearance of ketone bodies in the urine was of more serious significance. In 1912, before the Glasgow Obstetrical and Gynecological

Society, Williams modified his statement in a manner which still holds true, namely, that the increased proportion of ammonia to total nitrogen in the urine of pregnant women who are suffering from continued vomiting is of grave significance, whether due to starvation, or as an index of renal or hepatic failure.

The whole question of the nitrogen partition in normal and abnormal pregnancy is still a subject for investigation. Of the non-protein nitrogen on the katabolic side, in addition to ammonia and urea, there is an undetermined fraction. The ratio of these elements has important bearing as evidence of metabolic disorder. Simultaneous examination of the blood and urine for these products should be done on each case, but can only be properly done in laboratories associated with the better class of hospitals. The results, when interpreted by a well-informed biochemist, will assist the clinician in his course of treatment.

Clinical Course.—True toxemic vomiting may begin early in pregnancy, in an insidious manner, with the vomiting and nausea which usually occur becoming more and more severe as time goes on, or it may assume at once a more fulminant course. In the latter case, after a few days of ordinary "morning sickness," the patient may begin to raise a vomitus which contains a black, coffee-ground material, after which she soon passes into coma and dies within a week or ten days of the onset; during this time there has been no great wasting of the tissue nor loss of subcutaneous panniculus. In the more chronic form there is a pronounced period of excitation, alternating with periods of torpor and, later, coma. Beside this there frequently occurs a more or less marked tinge of jaundice, with tenderness over the liver; rarely do convulsions supervene. It has always been taught that fever accompanies this toxemia; unquestionably albuminuria is a constant finding. Emphasis has been placed on the rate and hypotension of the pulse of the patient. If the anhydremia and toxemia persist, the pulse becomes rapid and thready. Recovery has been noted where the rate exceeded 120, but occasionally fatal cases have been observed where the rate did not reach 100. There accompanies some of these chronic cases a peripheral neuritis with characteristic disorders in peripheral sensation and mobility and, in addition, trophic changes. Job, in 1911, collected 16 such cases from the literature.

Prognosis.—In the cases where the psychic element has been an etiological factor, the prognosis is particularly good, and prompt relief follows any of the simpler forms of therapeutics, while, in the true toxemic vomiting, active treatment may be instituted too late and these cases give rise to a high mortality. The presence of severe vomiting in one pregnancy is usually followed by vomiting in subsequent pregnancies. However, it is less likely to be of a grave nature and due rather to the psychic element brought about by the ending of the first pregnancy.

Treatment.—The adoption of proper hygienic methods of living and regulation of the patient's dietary regimen, together with enough laxative to correct the constipation, is, in the majority of cases of morning vomiting, all the therapy that is needed. Physicians have shown a tendency to belittle the vomiting of pregnancy and to classify it as inevitable. In lieu of this attitude the physician should insist that vomiting is not an essential accompaniment of pregnancy. Great attention should be paid to the minutest details of the patient's mode of living, proper exercise, proper mental occupation, and proper hours of rest. Before lifting the head from the pillow in the morning the patient may be advised to eat one dry cracker or piece of Zwieback, or a Bent biscuit, such as is eaten after dinner with cheese. Sometimes this is sufficient to allay the tendency toward vomiting; if such is not the case, an attack of vomiting may ensue as soon as the patient arises. Having emptied the stomach such a patient frequently can proceed to eat her usual breakfast, which is retained. Care should be taken to advise all these patients to eat small amounts at frequent intervals throughout the day, it being my custom to advise six small meals instead of three large ones. It is useless to give such general directions as are here recorded, but in each instance every move of the patient throughout the day should be specified by the physician and written down on a schedule, as though each individual decision that he makes has an important bearing on the case. The patient is impressed with the fact that she must follow with fidelity each of the details the physician has mentioned. As soon as the patient's vomiting is in any measure relieved, the physician must increase the fluid intake, and thereby promote the elimination of the toxins.

By attention to such details, a large number of cases will be relieved and obstinate vomiting forestalled. If, however, by reason of the fact that such attention has not been given to the patient, she is first seen in a condition of inanition, and more urgent measures are required, it then becomes of first importance to differentiate between the vomiting of reflex, psychoneurotic, and true toxemic types.

From a single observation of the patient it is not possible to distinguish between mild and grave types, but each patient must be studied and the diagnosis based on the findings in that individual instance. The physician must treat each tactfully and energetically as soon as she consults him with the complaint of vomiting of pregnancy. A thorough physical examination is the first requisite, in order to discover any possible anatomical lesion which may cause reflex irritation. If such a lesion can be demonstrated it should be corrected at once; while a failure to discover such a possible cause will encourage the patient. Little can be gained by the exhibition of drugs to allay the symptoms of nausea and vomiting, for these patients cannot tolerate much medicine by mouth, and the irritation of the stomach is not local, but due to a constitutional abnormality. However, cerium oxalate (gr. v.) in capsule, silver nitrate (gr. ¼), cocain and bismuth have been suggested. I find in my records that the following formula has proved useful at times:

℞

Cocain muriatæ	gr. ¼	02
Acidi hydrocyanici dil.	m. ii	1
Cerii oxalatis	gr. v	3
Aquæ menthæ piperitæ, q. s. ad	fʒi.	4

One dose, to be administered in a small amount of iced water, and repeated every four to eight hours, as necessary.

The very fact that there are so many suggestions in the literature as to therapy brings one to the conclusion that there is no specific line of treatment which is uniformly successful. The use of corpus luteum extract injected hypodermically is a case in point. J. C. Hirst found this therapeutic measure quite successful and many others have been enthusiastic over its effectiveness. These advocates and my personal experience with the remedy prove that it is successful in some cases of vomiting. But there has been no discrimination between the psychic cases and the true toxemias of a severe grade. I feel that this or any like remedy, in conjunction with the more general maneuvers, will relieve about the same proportion, while about 10 per cent of all cases of vomiting will resist any such therapy. Similar experiences and similar results were met with by Fieux in 1912 and by those who followed Mayer's treatment—the injection of from 10 to 20 c.c. of serum from a normally pregnant woman. This simply means that the majority of the cases are of the psychic type and respond to such therapy, while the true toxemias do not respond to any specific line of treatment yet suggested.

As I have already indicated, the most important move in handling one of these cases is absolute rest in bed in an institution away from the family and away from all external stimuli of an irritating nature. With a sympathetic and just but firm medical attendant and a competent nurse, isolation is to be desired in all of these cases. In the first place, reposition of a retroverted uterus, the removal of an ovarian tumor or some other peripheral irritation will relieve many cases. Secondly, suggestion and autosuggestion, as well as therapeutic efforts to dilute the toxins and promote elimination, are sufficient to relieve a large majority of the remainder. That small group of cases which persist in vomiting despite all the simpler remedies must be watched with greatest care.

The patient is moved to a quiet, semidarkened room to which no visitors are allowed. Nothing is permitted by mouth except an occasional piece of ice on the tongue. Fluids and medication must be administered by bowel or by hypodermocylsis. A graphic record of the temperature and pulse should be maintained with readings at no longer than four-hour intervals, and the total intake and output of fluids recorded. At once 1,000 c.c. or more of normal salt solution is allowed to run lateral to the breasts into the axillary spaces. The resident staff of the Woman's Clinic at Yale are convinced that large hypodermoclysis needles enter the inner surface of the thighs with less pain than under the breasts, that the solution is absorbed equally rapidly, and that the alternate use of the two areas is less damaging to the tissues. Therefore, we introduce at least 2 liters of fluid daily in one or the other region. In addition, the bowel is emptied by a cleansing enema and after a period of rest for two hours a proctoclysis of 300 c.c. of tap water is injected and repeated at three hour intervals. In lieu of plain water for the proctoclysis, one may profitably substitute a 5 to 10 per cent glucose solution or a 5 per cent bicarbonate of soda solution. At once the desiccation is relieved, the skin loses its dry, desquamating appearance, and becomes firm and moist. The patient becomes brighter, takes more interest in the treatment and grumbles at annoyances. On the second or third day of such treatment it has been my experience that sips of water will be retained when taken by mouth and the patient will ask for food. Fluids by mouth are not always well borne and often must be limited, but I never hesitate to meet the patient's whim with food as attractively prepared as it is possible to obtain. If in spite of such careful treatment the patient continues to manifest apathy, indifference, personal carelessness, drowsiness, disorientation or graver mental states, it is of serious moment and is pathognomonic of a profound true toxemia. Another serious phase not infrequently met is a temporary alleviation of the symptoms under treatment which leads to a too early relaxation of the restrictions and cessation of metabolic studies. These cases relapse in a week or two and suddenly sink into a profound toxemia, from which they do not recover. This phenomenon was recorded by Dubois, and similar instances are reported by Williams and others. I have seen 2 such cases which had been treated elsewhere and improved, but which relapsed and were brought to our clinic in a moribund state.

When the patient is first isolated and the metabolic study begun, a single specimen of urine is examined, but thereafter the measured total 24-hour specimen is collected and careful daily analyses made. Albumin, acetone, diacetic acid and sugar are quantitatively measured; the ammonia-nitrogen ratio determined, the blood sugar and blood urea likewise quantitated, together with a renal function test by phenolsulphonephthalein. As long as the ammonia-nitrogen ratio persists within the limits of normal, provided the sugar threshold is not lowered and the clinical symptoms do not progress, an expectant course may be pursued. However, in the presence of a rising or persistently high (20 + per cent) ratio, the condition is grave, is due either to starvation or to a profound toxemia, and active interference is indicated. Besides this laboratory guide, active interference should be instituted on the appearance of a falling blood-pressure that is persistently below 100 mg. of mercury, together with a pulse rate that is persistently over 120 beats per minute, together with the appearance of a slight tinge of jaundice, torpor, coma, or coffee-ground vomitus.

When the diagnosis of true toxemia on the basis of these findings is made, the treatment par excellence is therapeutic abortion, which should be performed by the simplest and smoothest available surgical procedure. Chloroform should not be used as the anesthetic. For a short time after operation no effort should be made to give the patient food by mouth.

ACUTE YELLOW ATROPHY

This disease is characterized by a rapid and extensive destruction of liver tissue which manifests itself through sharp pains in the epigastrium, vomiting, purging, headache, jaundice and coma. The condition is rare, but 60 per cent or more of the collected cases have occurred in pregnant women. The disease usually appears in the latter months of pregnancy, but has been reported in the first two months and occasionally is seen in the puerperium.

Clinical Course.—The onset of the disease is sudden and the course may be acute or protracted. Because of these characteristics, as well as of the similarity in symptoms, a diagnosis of acute phosphorous poisoning is often made. In sequence the symptoms appear in the following order: sharp abdominal pain, vomiting and purging, shortly followed by torpor and jaundice, coma, and occasionally convulsions. The patient may fall into labor and expel a dead fetus. In the less rapidly progressing cases the area of liver dulness, which for the first two days may be increased, rapidly diminishes in size. There is slight alteration in the pulse and in the temperature of the patient until the anhydremia and tissue death become pronounced. As a rule the progress of the disease is so rapid that emaciation is not severe. The urine early shows albumin, a diminished urea output and a relatively high ammonia excretion.

Etiology.—We are entirely ignorant of the primary etiological factor in acute yellow atrophy, but, just as was said in discussing pernicious vomiting, it is obvious that the liver and kidney manifestations are secondary.

Pathology.—In this disease the most rapid and extensive autolysis of body tissue that is known takes place. At autopsy the liver may weigh less than one-half of the normal. The organ appears shrunken, there is a wrinkling of Glisson's capsule. The color is a deep yellow, with regular, fine, dark plum or red mottling. On close observation of the cut surface each lobulation is distinct with a purplish red center and a yellow periphery. Fat is so evident that the knife blade seems greasy after sectioning the organ.

Histologically the lobule shows a central necrosis with a wide midzone of marked fatty degeneration and a few apparently normal cells about the periphery. The periportal spaces and the cells in the immediate vicinity are apparently unchanged.

The kidneys show recent cloudy swelling of the epithelium of the convoluted tubules with considerable desquamation. In the lumina of the convoluted tubules are débris and cell casts. The glomeruli are not specifically affected.

Diagnosis.—The similarities between and the appearance of intermediate types of the two diseases give some weight to the belief that pernicious vomiting and acute yellow atrophy are manifestations of a similar toxic process. They arise in pregnancy under similar conditions, pursue much the same course, present similar pathological lesions and identical urinary findings. Ewing suggested that the rapid autolysis of liver cells might be due to the extravasated bile generated from some specific form of intestinal putrefaction. It is true that in the one case the toxin has a strong emetic principle, is more likely to occur early in pregnancy, and presents less destruction of liver tissue but more general body wasting for the relative duration of the disease; while in acute yellow atrophy the incidence is late in pregnancy, or the puerperium, jaundice appears more promptly and is the significant symptom, and the liver may decrease by one-half in a week's time.

That eclampsia and acute yellow atrophy are more often confused or are of identical origin is not so logical. Jaundice is suggestive of acute yellow atrophy; then, too, in this condition the blood-pressure is below normal and the urinary findings are distinct. As I have said, however, if a case is not seen until coma or convulsions have supervened, a differentiation between eclampsia and acute yellow atrophy might only be made at autopsy.

Prognosis.—The outlook is always grave, the determining factor, of course, being the extent of hepatic necrosis which can only be surmised; therefore recovery should be hoped for rather than expected.

Treatment.—As soon as the diagnosis is made the uterus should be emptied in the manner least harmful to the patient and as rapidly as is consistent with safety. The toxins may be diluted and eliminated by the employment of hypodermoclysis and forcing fluids by mouth, diaphoresis by external heat and mild purgation by magnesium oxid or phenolphthalein. Diuretic and diaphoretic drugs are uncertain and as a rule harmful. Obviously, if the condition has arisen in the puerperium, only the eliminative treatment is available. However, the probable cause of the metabolic disturbance, namely, the fetus, has been removed and the chances of recovery are better.

NEPHRITIC TOXEMIA

In view of what has been said in general about the burden of pregnancy on the maternal metabolism it is easy to understand that any constitutional disease which has impaired kidney function may seriously influence subsequent gestation. Indeed I have several case records which tend to show that there are women whose kidneys compensate under ordinary conditions but who cannot bear the added strain of pregnancy. Such a group is hard to identify in the interval, but, when a patient with a chronic nephritis becomes pregnant, the observant physician can soon demonstrate an aggravation of the condition. Hypertension early becomes alarming, casts appear in the urine, together with a trace of albumin by the boiling or nitric acid tests, the arteries in the fundus of the eye compress the veins and show a gray line of thickening with increased tortuosity. By the fifth or sixth lunar month the danger point in blood-pressure (150 mm. Hg.) has been reached, the urinary output has diminished and the specific gravity has become so low as to demonstrate little excretory ability. Further, the face, hands and feet show edema and petechial hemorrhages appear in the eye-grounds. Such a patient may have few or no subjective symptoms, save edema and headache, and, if the condition has not been recognized, may pass suddenly into coma, with or without convulsions, from which recovery is slow and death is by no means rare. In these cases many red and white infarcts of the placenta are common and one of the suggested causes for some instances of premature separation of the normally implanted placenta is chronic nephritis. With the occurrence of either of these conditions in the placenta the risk to the fetus is materially increased. Indeed, in our clinic, death of the fetus in utero from chronic nephritis in the mother is equally common with syphilis. The two combined have caused the majority of fetal deaths. As a general rule it may be said that nephritic toxemia plays the most important rôle from the middle trimester on, while syphilis and eclampsia are most likely to evidence themselves in the last three months of pregnancy. The death of the fetus in utero and its expulsion acts as a protective mechanism for the mother.

Differential Diagnosis.—It is sometimes impossible to differentiate between impending eclampsia or toxemia due to the pregnancy, and nephritic toxemia or a retention of the maternal and fetal waste products due to the diminished renal threshold. It may be said that, in general, a more marked hypertension exists without other symptoms in the nephritic case than in impending eclampsia; however, such a statement would not avail in the wide zone where the blood-pressure readings coincide.

Both give:

Headache
Edema
Disorders of vision

Hypertension
Albuminuria

Coma
Convulsions

And differ in the following characteristics:

Impending Eclampsia	Chronic Nephritis
Generalized puffiness of face, hands, feet and abdominal wall.	Marked edema, especially under eyes and in dependent portions.
Generalized gray and glistening edema of the retina.	Tortuous ocular vessels and petechial hemorrhages.
Total amount of urine diminished.	Total amount of urine may not be below normal.
Epithelial and coarsely granular casts.	Finely granular and hyaline casts predominate.

On the appearance of coma or convulsions eclampsia and nephritic toxemia cannot be differentiated save possibly by the opthalmoscope. Nor is the treatment at that time different in the two conditions. However, upon successful elimination of the added burden, the product of conception, and effective response to stimulation of the patient's emunctories, a case of eclampsia will recover and the blood-pressure return to normal within a few weeks. On the other hand, a case of nephritis will return to a state of moderate hypertension and compensation, but evidences of permanent kidney damage will remain and probably be more pronounced. Rarely the differentiation can be made only at autopsy.

Prognosis.—If the case of pregnancy associated with chronic nephritis escapes coma and convulsions under the treatment to be described, the prognosis as regards this particular pregnancy is not unfavorable. However, the strain of pregnancy will increase the kidney damage and shorten the patient's life. The prognosis for the fetus is not so favorable, as has been explained. It can be inferred from the data presented that the earlier in the period of gestation the nephritic toxemia manifests itself, the less likely the two patients are to survive.

Treatment.—One of the most difficult situations met in medicine arises when the family physician advises a young woman who has just recovered from scarlet fever or acute rheumatic fever, and who has a permanent limitation to her renal efficiency, that she cannot be subjected to the strain of childbearing. Despite this advice, or more often through lack of a conscientious attendant, such a patient becomes pregnant. The limitation of proteins in the diet and special attention to elimination by the bowel are the first methods of meeting the condition. Fluid intake by mouth and hypodermoclysis cannot be so effectively practiced without attention to the output, for it is easy to "waterlog" such patients. Either the vessel walls are permeable to fluids, or the tissues call the fluid out of the blood column. Furthermore, the kidneys cannot eliminate the excess fluid or toxic products with anything like normal efficiency. Strict limitation of exercise will diminish the bulk of waste products and somewhat limit the tax on the kidneys. If the religious scruples of the physician and patient permit it, therapeutic abortion may be done on a patient who shows signs of kidney decomposition immediately before pregnancy and whose condition becomes aggravated as soon as pregnancy supervenes. This is not advisable until an adequate test of the effect of pregnancy and the concurrence of a reliable internist, who can verify the functional tests, are obtained. Such a therapeutic procedure may be justifiable once, but, after careful explanation of the facts in the case to the family, a similar operation is never justified in a second instance. Occasionally after one unsuccessful effort to complete a pregnancy, especially if the nephritic changes become progressively more severe, termination of a second pregnancy by abdominal hysterotomy may be allowable, and sterilization may be performed.

In the less obvious type of case a more conservative treatment is recommended. At the first appearance of signs of nephritis, moderate hypertension with some edema and fine granular or hyaline casts, the patient should be put to bed on a milk and water diet (broths and soups from meat stock are harmful). As the symptoms are relieved and the function compensates, graded exercise and slow addition to diet (salad, whole wheat bread and low protein vegetables) are allowed. In the event of continued improvement the last things to be allowed are eggs (one per day). Meat, fish and poultry are never permitted. Fluids are forced as the edema subsides. If the patient is particularly desirous for the pregnancy to continue she will coöperate well. After the period of viability, induction of premature labor may be justified in the event of a sudden aggravation of the symptoms, for a premature child may more likely survive than a child subjected to grave maternal toxemia throughout the latter months, especially in view of the high mortality in utero.

If the nephritic patient has been neglected through her own or another's shortcoming, and is not seen until convulsions or coma ensue, the treatment is the same as for eclampsia, and had best be detailed under that chapter; suffice it to say that copious phlebotomy, sweating and guarded injection of fluids form the most rational treatment.

IMPENDING ECLAMPSIA

A literal interpretation of the term "eclampsia" may be reserved for the cases in which convulsions actually occur, while the long chain of symptoms which precede the seizure, and which are amenable to treatment, are spoken of as "impending eclampsia." It should be understood that this does not imply that there is a separate toxemia with distinct etiology in each of these instances, but rather to convey the idea that they represent varying degrees of the same condition and that the graver will supervene, if the milder prodromal complex is not rigorously treated. With the same intent other authors have referred to the latter group as the "toxemias of pregnancy *without* convulsions" and "preëclamptic" toxemia (the *eclampsisme* of the French).

It is my belief that eclampsia is in great part a preventable disease. Although there are occasional instances cited of "fulminant" eclampsia in which no prodromal symptoms have been elicited, subsequent careful analysis of the record and further questioning of the patient or her relatives usually afford suggestive signs which might have enlightened the attendant. Occasionally, too, certain of these cases clinically diagnosed as fulminant eclampsia have disclosed at autopsy other lesions as the cause of convulsions and death. One such patient who came under my observation recently died of a brain tumor in the occipital region. Therefore, while there may be rare instances when the onset can not be foreseen, nevertheless the premonitory signs, grouped together as "impending eclampsia," are the most frequent of the toxemias met with in pregnancy. The prodromal symptoms are particularly common in primiparæ, in twin pregnancies, in illegitimate pregnancies and in similar conditions where the burden on the mother is more than the usual case presents. The symptoms appear in the latter part of pregnancy, and are more likely to be met as term approaches.

Adequate prenatal care consists of accurate mensuration of the pelvis, of a routine Wassermann examination, and of frequent examinations to detect the onset of pathological conditions. Not the least important of these examinations are those directed toward forestalling impending eclampsia. Toxemia of the nephritic type and preëclamptic toxemia are similar, and the conditions should be suspected as soon as the patient complains of headache, lassitude or edema. Routine examinations of the blood-pressure ought to be made at biweekly intervals. One of the best prodromal signs of toxemia is a gradual rise in systolic pressure. Mild headaches may progress to more severe and more constant ones; scotomata, muscæ volitantes, and, later, amaurosis occur; the total amount of urine is diminished; finally, violent epigastric pain is experienced; occasionally hallucinations, flashes of light before the eyes, and convulsions supervene.

The appearance of albumin in the urine, and the presence of edema, and an elevation of blood-pressure, are the criteria upon which a diagnosis of impending eclampsia is based. Of the three, the blood-pressure readings are by far the best clinical guide, and the diagnosis is not faithfully made without the presence of two of these three cardinal symptoms. When blood-pressure examinations are taken throughout pregnancy, the normal experience is that during the first trimester the tension is somewhat lower than normal. From the middle trimester to term the systolic reading rises from 118 to 128 mm. Hg. Due allowance must be made for individual variations and those from extraneous causes; single readings should not be deemed conclusive. Slemons and Yudkin have established a blood-pressure curve for normal cases during pregnancy, and, in the presence of headaches, lassitude, edema, or albumin in the urine, blood-pressure readings should be taken daily. On demonstrating a tendency for the blood-pressure to rise above the normal level, impending eclampsia must be regarded as a probability, and the first measures in its treatment instituted.

Certain qualifications must be made in regard to the other symptoms of toxemia. Headaches and malaise may be due to an aggravation of chronic constipation which is so common at certain stages of pregnancy. If unrelieved, this condition will aggravate, if not cause, profound toxemia, and treatment directed toward the relief of this condition is a primary move in meeting all toxemias. Likewise, edema of the feet and legs may be due at times to pressure on the iliac veins by a gravid uterus at the pelvic brim. On the other hand, intermittent and progressive puffiness of the feet, dorsum of the hands, face and fingers is of more serious significance. Thirdly, as soon as the uterus begins to enlarge there is an increase in the vaginal secretion, which continues throughout pregnancy. This secretion is cervical and contains, as well, desquamated epithelium from the vagina. All voided specimens are contaminated by this secretion and consequently give a positive reaction for albumin, which is increased as pregnancy proceeds. Obviously this can never produce a marked reading by quantitative methods, but it is always well to secure, under aseptic precautions, a catheterized specimen of urine before laying too much stress on the presence of albumin as a symptom of impending eclampsia.

Prognosis.—The prognosis in impending eclampsia is, as a rule, good. Depending upon the assiduity with which the physician has applied himself to the treatment of the case and to the coöperation of the patient, the condition may be controlled until the termination of pregnancy. However, permanent damage to the kidneys is frequently demonstrable after delivery or in a subsequent pregnancy; consequently the majority of these cases are nephritic in type. There is an opinion that impending eclampsia produces a moderate immunity and is not likely to recur in subsequent pregnancies. However, this statement must be guarded. Even if the nephritis subsides after delivery and the kidneys apparently regain compensatory function, it is doubtful if they have as high a reserve function for future emergencies as they formerly possessed.

Treatment.—The prophylactic treatment of this type of toxemia begins with the directions given the expectant mother when she first consults her physician. The particularly important items are: (1) those regarding diet, bathing and clothing; (2) attention to constipation, edema, headaches, dizziness and other mild symptoms that may arise; and (3) emphasis on regular examinations of the blood-pressure and urine.

Early in pregnancy there is no indication to restrict the diet; indeed, an expectant mother should be encouraged to eat light meals at frequent intervals. She should, however, avoid any foods which have disagreed with her on previous occasions. Fruit, especially cooked fruit, is beneficial. In my practice I do not countenance raw pears, bananas or berries, for many people have idiosyncrasies to these fruits, and in cities they are often sold and served slightly under-ripe or over-ripe, and are in either case apt to cause an acute gastro-intestinal upset. Since milk is later to play so important a part in the diet, I encourage all my patients to cultivate a liking for this form of food, laying stress on malted or peptonized, soured or buttermilk in those instances where raw milk is objectionable.

For the latter half of pregnancy, by means of a low protein diet in which meat is reduced to a minimum, but in which salads of all kinds and leguminous vegetables are required daily, and the fluids forced, the burden on the mother's excretory functions is reduced and no deleterious effect on the fetal development has been noted. For the hyperchlorhydria, which is so frequent an annoyance in late pregnancy, nothing is so satisfactory as a rigid "Sippy" diet of cream, butter and olive oil. This symptom may be further relieved by the administration of bismuth subcarbonate and magnesium oxid. It is not my practice to prolong the intervals between changes in the Sippy diet to three days, as advised for patients with gastric ulcer, but additions may be made on succeeding days, as the symptoms subside.

It is uncertain how much waste material is eliminated through the skin. However, a certain amount of fluid is lost in this manner, and such a loss can be increased by stimulative diaphoresis. The simplest method of promoting activity of the skin is by frequent bathing. I direct my private patients to take a warm bath daily (85° to 90° F.) at a specified time of day, depending on the reaction of the patient to the warm bath. For instance, if such a bath arouses the patient, I recommend that it be taken late in the afternoon, before dinner. If, on the other hand, it makes the patient drowsy and relaxed, it had best be taken just before retiring.

It is particularly difficult nowadays to succeed in adequately clothing expectant mothers. Formerly, I specified a wool or silk-and-wool suit of underwear next the skin. This rule was more honored in the breach than in the observance; therefore, I lay less stress on the underclothing and now require a woolen one-piece dress hung from the shoulder during the autumn and winter months, and more adequate protection while out of doors.

Constipation is constantly an annoyance during pregnancy. If the patient has maintained bad habits in this regard previous to pregnancy, the condition is aggravated and the difficulties amount to serious interference with elimination. In our clinic we place in the hands of each expectant mother the brochure prepared for the Children's Bureau by Mrs. Max West on "Prenatal Care." This pamphlet contains a recipe for the preparation of an infusion of senna with stewed prunes. Some such dessert is prescribed routinely in our dietary régime. Some standard preparation of mineral oil free from irritating hydocarbons is added when the senna-prunes preparation is not effective. Unless it is required, we abstain from prescribing another laxative. If such a drug becomes necessary, we choose between the fluid extract of cascara and some preparation of phenolphthalein. Most of the proprietary pills contain strychnia, and the layman believes that if one such pill is not sufficient two may be, and three not without benefit. By this time the patient has consumed 1-20 gr. or more of strychnia and wonders at her restlessness and the child's activity in utero. Habitual use of enemata to relieve atony of the lower bowel may be indicated in extreme cases, but the risk of forming a habit that will last and the danger of inducing premature labor must always be borne in mind.

Without alarming the patient, her attention must be drawn to the necessity for reporting mild symptoms which point toward impending toxemia. These symptoms are dizziness, frontal or occipital headaches, especially those that appear on arising in the morning, and, lastly, the appearance of edema of the feet, hands and face. The patient is instructed to report once every month for examination until the seventh month, every two weeks thereafter until the tenth month, when she must report every week. At each of these visits she is told to bring a sample of the total urine passed for the preceding twenty-four hours, together with a record of the amount from which this specimen was secured. More frequent examinations are required if the prodromal symptoms of eclampsia manifest themselves.

It would be presumptuous to specify detailed minutiæ, had this procedure not proved effective. Criticism of detailed prenatal care, such as has just been outlined, has hitherto been based largely on the objection of the private practitioner to subject his poorer class of patients to an expensive and detailed mode of life. Justification for this routine is based on the fact that such coöperation as I have been able to secure with the help of a prenatal nurse and the members of our staff has resulted in only one case of eclampsia in the last 1,200 patients cared for by the Outside Obstetrical Service at Yale. The clientele was of the poorest and largely of foreign birth. In the same class of patients prior to that time the incidence of eclampsia was not infrequent. If, at one of the regular visits, the patient shows a rise in blood-pressure to 140 mm. Hg. and edema, or if a sample of urine shows an increasing amount of albumin, she should be told to rest in bed, to drink copious amounts of water or milk, and to avoid solid food. The urine should be tested quantitatively for albumin by means of an Esbach albuminometer; probably ½ gm. per liter is within the limits of normal for a voided specimen. The physician should also prescribe a brisk saline laxative of magnesium sulphate or sodium phosphate (granular). The urine examination should be repeated daily, the fluid intake and output recorded, blood-pressure readings taken twice daily and the Esbach readings set up on a specimen of every 24-hour collection of urine. When advocating an increased fluid intake, it should be realized that there is a limitation to the quantity of milk and plain water which the patient can consume; but any addition to the water, such as lithia, cream of tartar,[1] or lemonade, will give the water a pleasant taste and enable the patient to consume a larger quantity. Such a plan of treatment is usually sufficient to hold the toxemia in check. If in spite of such treatment any of the symptoms persist or increase; for instance, if the systolic pressure rises to 150 mm. Hg., or the quantity of albumin increases to 4 gm. per liter, phlebotomy and hypodermoclysis must be done. Careful notation should be made of the other subjective signs of impending eclampsia, headache, epigastric pain, disorders of vision, a sudden exaggeration of the systolic pressure above 150 mm. Hg., or a further rise in albumin excretion. In the presence of these signs there is sufficient indication for the induction of the premature labor.

In terminating the pregnancy the least drastic operative procedure is always to be preferred. I am strongly averse to the routine practice of terminating labor by cesarean section in patients with toxemia; those with impending eclampsia do not bear general anæsthesia well, their tissues do not heal kindly, while the risk of edema of the lungs is great. Moreover, the added strain and shock of operation increases the gravity of the prognosis.

The most satisfactory method of inducing labor is by the introduction of a Wales' bougie or a Voorhees' bag. The former softens the cervix and subsequently the balloon may be employed to stimulate pains and hasten dilatation. Following such a procedure the patient usually expels the product of gestation spontaneously. Occasionally, when the cervix is fully dilated, spontaneous expulsion is slow, and labor may be terminated (under nitrous oxid and oxygen anesthesia) by a simple obstetrical operation, such as low forceps. The onset of an eclamptic seizure is not altogether obviated by the delivery, and the toxemia must be combated during the puerperium until the edema disappears, the systolic pressure has returned to normal, and albumin has disappeared from the urine.

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[1] The advisability of giving tartrates is dubious in view of Underhill's work showing that they irritate the kidneys.—Editor.

ECLAMPSIA

The convulsive attacks, which give the disease its enduring name, are but a symptom which may arise in this condition, and it must be understood that their occurrence is but the final expression of a disease which has existed already over a considerable period. Disregard of this fact has led to the diagnosis of eclampsia only in those conditions where convulsions have supervened, while undoubted instances of death from this toxemia without actual convulsions have been reported (Schmid, 24 cases). Moreover, convulsions from other causes are occasionally associated with pregnancy. Therefore, eclampsia is, properly speaking, a toxemia characterized by certain specific pathological findings, and in most instances is manifested by clonic and tonic convulsions, loss of consciousness, and coma. The fetal and maternal mortality is high; in long series of cases in the continental clinics reaching about 70 per cent for the former and 30 per cent for the latter.

It is very difficult to determine authoritatively the incidence of eclampsia, for few private practitioners can attend sufficient cases to acquire a comprehensive series. Moreover, hospital records show too high an incidence due to the fact that cases arising in private practice, which otherwise would have remained at home, are immediately institutionalized. Despite these sources of error, it is estimated that eclampsia occurs once in every 500 labors at large, and once in 100 labors in large maternity clinics. The statistics of the continental clinics cover a longer series and show a slightly lower incidence—Veit 0.6 per cent (German clinics); Knapp (Prague) 0.53 per cent; Reinburg (Paris) 0.34 per cent—than those in the United States—Newell (Boston) 1.17 per cent; Williams (Baltimore, 1912) 1 per cent. The variable factor in these observations involves the hospitalization of a larger group of normal multiparæ in the European clinics than as yet has been attained in the United States.

Eclampsia is of more frequent occurrence during the last trimester of pregnancy and is more likely as gestation nears its close. However, cases have been reported as eclampsia in the third (Zweifel) and fourth months (Maygrier and von Herff) of pregnancy.

According to statistics from maternity clinics, primiparous women are much more likely to suffer from eclampsia than are multiparous. On the other hand, I have seen a case of undoubted eclampsia in the twelfth pregnancy where the preceding pregnancies had not been complicated by any metabolic disorder.

Casamayor called attention to the varying incidence of eclampsia in different years. Apparently the incidence of eclampsia is not quite so high now as it was a few years ago; nevertheless, it is sufficiently frequent in the United States to be of serious import. There may be a geographic and seasonal variation to eclampsia which bears some relation to climate and temperature. While in practice in Oregon I saw only 2 cases of eclampsia, and my associates who were in California during the same period report a number of cases of preëclamptic toxemia, but no actual cases of convulsions. Grenfell and Curtis say there is no eclampsia in Labrador. On the eastern seaboard of the United States there is a notable increase in eclampsia during the spring and autumn months. This may have something to do with the climatic conditions, but as yet too little is known of the other variable factors such as diet, clothing, intelligence in following advice, etc., to emphasize unduly any evidence we possess as to seasonal or geographic incidence.

Clinical Course

The clinical picture which may arise at any time during the latter half of pregnancy, during labor or during the puerperium, is striking. While customarily preceded by the prodromal manifestations mentioned under the heading of Impending Eclampsia, the first symptoms observed by the patient may appear like "a bolt from the sky," with sudden sharp, epigastric pain and blinding flashes of light before the eyes. For a moment the patient is still, with a fixed stare, then the eyes roll from side to side, the mouth twitches and the face becomes distorted. The head, arms, legs and body successively show a clonic spasm. Occasionally these clonic spasms suddenly become tonic and the patient becomes rigid in opisthotonos. This change may occur so suddenly that the patient may project herself off the bed or strike herself on some nearby object with force enough to do serious injury. During the height of the spasm, the respiratory mechanism is held in abeyance, the patient becomes markedly cyanotic, the mouth is filled with mucus, the tongue is swollen and frequently injured by the teeth during the spasm of the jaw. After a duration of from one to two minutes, when the picture is one of almost immediate exitus, suddenly the spasms subside, respirations of a stertorous fashion begin, the opisthotonos disappears, the patient moans and breathes rapidly, and a period of quiet and rest may ensue, or wild delirium until the next convulsion occurs. The patient may go on from convulsion to convulsion, with periods of diminishing duration between. During the intervals she may be comatose, although extremely sensitive to external stimuli of light or noise or handling. Symptoms of the onset of labor early manifest themselves, or, if labor has already begun, become more pronounced. Under these circumstances the convulsions may recur, due to the stimulation of the contractions. Recovery has been reported after as many as thirty convulsions. The highest number of seizures noted was above eighty, followed by death. Apparently the number and severity of the convulsions has no relation to the degree of toxemia, but is a valuable guide as to the efficacy of the therapeutic measures employed. Before the convulsive attacks the skin is dry, the whole body becomes edematous, particularly in the subcutaneous tissue of the face, hands and feet. Frequently the orbital ridges, bridge of the nose and zygomata are masked, so that the appearance of the patient is remarkably changed. There is a diminished amount of urine or a total anuresis. When a specimen can be recovered by catheter it is of a typical dark, concentrated, smoky character, containing a high albumin content, and numerous epithelial and coarsely granular casts. Commonly there is hypertension; the radial pulse is of a high, bounding, and noncompressible type.

In the previous chapters on Impending Eclampsia I have said that the three cardinal symptoms are edema, albuminuria, and elevated blood-pressure; but if any two of these three are demonstrable, it is sufficient for a diagnosis. The absence of one of the three symptoms is occasionally noted. For instance, I have seen a case of eclampsia in which convulsions occurred with a blood-pressure of 120, and, again, a seizure occurred in another case which showed only a trace of albumin. The urine occasionally does not show an unusual amount of albumin until the first seizure has occurred. Varying degrees of edema appear in equally grave cases, although it is commonly stated that a better prognosis may be given in those instances where it is marked. Nevertheless, of the three, the blood-pressure is the best prodromal sign and guide to therapeusis.

Death may occur during a seizure, in the interval between, or even after the subsidence of convulsions. Usually it is due directly to edema of the lungs, apoplexy, or, after several days, to pneumonia or puerperal infection. There is unquestionably a peculiar susceptibility to infection in patients suffering from toxemia. Elevations of temperature to 104° F. are usual; in one of Williams' fatal cases the temperature reached 109.5° just before death. Such degrees of fever have been ascribed by Olshausen to the effect of the toxins on the thermal centers, while Zweifel believes the hyperpyrexia to be due to infection. The first theory is probably correct in those cases in which a notable hyperpyrexia appears early in the course of the disease, but the occurrence of fever following delivery and subsidence of the convulsions is probably due to infection.

Depending on the relation of the appearance of the convulsions to the onset of labor, three types of eclampsia are recognized. These are designated as antepartum, intrapartum and postpartum. Considerable confusion has arisen in the literature in regard to the relative frequency and gravity of these three types. This is largely due to the fact that a certain number of cases fall rapidly into labor after the first convulsion. On the other hand, many cases of impending eclampsia need only the stimulus of labor pains to develop convulsions. So that in either event the physician would determine with difficulty whether the labor antedated the eclampsia or the reverse. Eclampsia in rare instances may subside and the patient later be delivered. A dead, macerated fetus is usually the result, but cases have been reported in which living children were delivered after the subsidence of severe eclamptic seizures. One patient whom I treated for typical eclampsia recovered and was delivered six weeks later of a healthy child. It is the common belief that death of the fetus in utero has a favorable influence on the course of the disease in the mother, although Lichtenstein holds that the life or death of the fetus is without significance. Intrapartum eclampsia usually stimulates expulsive forces, thereby shortening the duration of labor. However, lacking facilities or trained attendants for operative methods of delivery, a patient suffering from either of the above types of the disease may die undelivered.

In postpartum eclampsia the number and severity of the convulsions is usually limited and, because of the removal of the suspected source of the toxemia, this type is commonly regarded as the least serious. Such a belief is not borne out by facts; the mortality rate is high. This may be explained rather on the hypothesis that a toxemia so profound as to affect the mother after delivery is more likely to cause her death.

Among the prodromal signs presaging an eclamptic attack have been mentioned scotomata, muscæ volitantes and girdle pains in the epigastric region. Other central nervous system phenomena occasionally manifested are severe frontal headaches and blindness. All these symptoms appear before the convulsion. Total unconsciousness follows the seizure for a longer or shorter period of time; and after recovery there is usually no recollection of events immediately antedating the first seizure. The blindness is due to a diffuse edema of the retina, which is distinctive of the disease, and which may lead to a detachment of a considerable portion of that membrane. However, this does not result always in a permanent impairment of vision, for in two instances observed in our clinic by Dr. Eugene Blake and myself reattachment of the retina occurred. Following eclampsia the heightened incidence of psychoses is so noticeable that the toxemia is regarded as the cause of a considerable number of cases of puerperal insanity. It is uncertain whether these psychoses depend upon the toxemia alone, or upon the puerperal infection which so frequently follows eclampsia.

Dienst and Barr and Guyeisse noted albumin in the urine of infants born of eclamptic mothers and, in such infants as came to autopsy, renal changes simulating those of the mother.

The differential diagnosis must distinguish preëclamptic toxemia from chronic nephritis, and, after the convulsion supervenes, from seizures due to strychnia poisoning, tetanus and uremia. If the patient is seen in coma, with no history of the convulsive seizure, diabetes as a cause of the coma must be eliminated. When seen for the first time in the convulsion, the differential diagnosis between nephritic toxemia and eclampsia may be made with the opthalmoscope, if it can be made at all. The characteristics of the urinary secretion may help, in that in nephritic toxemia the quantity of urine is not necessarily diminished; but the presence of hyaline and granular casts would point to a more chronic condition, while the highly concentrated diminished amount of urine typical of acutely affected kidneys, showing epithelial and coarsely-granular casts, is distinctive of eclampsia. In the case of strychnin poisoning and tetanus, the history and the type of seizure may be of some assistance; again, the urinary findings would not be so distinctive as they are in eclampsia. Obviously, diabetic coma is distinguished by the acidosis, the ketonuria and glycosuria.

Pathology

In 1903 Schmorl reported 70 autopsies on eclamptic patients, in which he specified three requisites for the diagnosis of eclampsia: (1) edema of the brain; (2) specific kidney lesions; and (3) specific liver lesions. Of these three, the changes in the liver he held to be pathognomonic. The liver lesions are eccentric or periportal in their distribution, and are more distinctive for eclampsia than are the central necrotic lesions for the early toxemias of pregnancy. I should say that the present thought among pathologists is that the periportal lesion of eclampsia must be present before the diagnosis of eclampsia can be made, though it perhaps is not the only disease in which such a condition appears. The findings of Schmorl correspond to those described by Ewing in the article referred to under Pernicious Vomiting and have been substantiated by subsequent pathological investigation.

Edema of the brain cannot be demonstrated with great facility at the autopsy table, nor can it be definitely diagnosed from histological specimens. The renal lesion consists of an acute inflammatory condition involving the convoluted tubules in which the epithelium is degenerated and missing in large areas. The glomerular involvement is less well marked. The involvement of the peripheral zone of the liver lobule consists of cell death, loss of the staining qualities of the nuclei, and some fatty degeneration, while the central portion of the lobule may be in perfect condition.

ETIOLOGY

Eclampsia seems to be a hepatorenal block accompanied by a concentration of the blood volume, together with a marked edema or extravasation of the serum into the tissues. Especially when affecting the brain, such a marked extravasation produces an increased intracranial pressure, together with hypertension in the cardiovascular system, the last manifestation being a convulsion. Any further dogmatic statement in regard to the causation of this condition is, at the moment, impossible. Slemons' investigation proved that there is little to the acidosis theory and there is no marked derangement of the protein metabolism. Since 1916, especially in the German clinics, a great impetus has been manifest in the study of eclampsia. Warnekros claimed that the absence of the husband, others that the reduction in protein intake and restricted diet, was the cause for a marked reduction in the incidence of eclampsia, which was noted in Germany during the period of the War. In a very well-balanced criticism of these theories, Lichtenstein has determined that there are so many other variable factors, such as bad transportation facilities, increased incidence of home deliveries, diminished incidence of hospitalization of the pregnant women, etc., that an apparent decrease in eclampsia is no more than proportionate to the general decrease in the birth-rate.

That the liver and renal lesions are secondary in eclampsia is practically universally accepted. As to the primary cause, Bory advances an unusual hypothesis, namely, that fetal toxins pass through a defective placenta and are admitted into the maternal circulation, where they set up this intoxication. The theory that eclampsia is an anaphylactic shock is disproved by a series of animal experiments done by Eisenreich on the complements contained in the blood of pregnant women and of those in labor. Zinsser proved that the toxemia is not a result of protein destruction. On the other hand, experimental proofs have been submitted which show that there is an increased destruction of blood-cells, together with an increased amount of hematin in the serum, while the proportionate amount of fibrin in the blood of eclamptic patients is decidedly increased; so that certain clinical findings analogous to serum hemoglobinuria favor an anaphylactic theory. Since all these theories are interpreted in the light of the several authors' favorite therapeutic measures, it is difficult to segregate theories of etiology from methods of treatment.

TREATMENT

My experience is thoroughly in accord with Ruge, namely, that despite all therapeutic efforts a certain and not small number of patients with eclampsia will die. This is due to the fact that a considerable damage to vital organs, such as kidney and liver, has been suffered before the symptoms manifest themselves, and before treatment is instituted. Certainly in those cases where there is a complication of lung or heart defects, any efforts at therapy are not as uniformly successful as they would be in cases that otherwise were perfectly well. It is to reduce the number in this group that prophylactic measures should be urged. With this in mind, I have carefully gone into the subject of the treatment of the prodromal signs in the chapter on Impending Eclampsia. Rest in bed, limitation of diet, guarded administration of alkalis, the forcing of fluids, and occasionally prophylactic venesection may early be resorted to, and even premature labor induced when the symptoms fail to subside or become more alarming under this expectant treatment. In accord with Dice, I lay particular stress on an examination of the eye-grounds. To this end, every practitioner should familiarize himself with the use of the ophthalmoscope, so that when the occasion demands he may be competent to distinguish the pathologic fundus oculi from the normal.

As diagnostic signs of impending eclampsia, Pacheco has recently described changes in the specific gravity and in the chlorid content of the urine. In treatment, he used copious injections of glucose solution. To meet the same need, Villaneuva has advocated copious intravenous injections of sodium bicarbonate solution.

After all, the major value in the discussion of the treatment of eclampsia revolves around the question of active surgical interference, in preference to temporary measures that are of a medical nature. With the development of aseptic surgery and the increased number of operative procedures, particularly cesarean section, there was a wide advocacy of that procedure in the handling of eclampsia. Undeniably, the majority of modern writers, especially those connected with competent university clinics, are condemning radical measures in the treatment of eclampsia. The only commendable claim for cesarean section in this condition rests upon the fact that competent surgeons can be found more frequently than well-trained obstetricians. The advantages claimed for delivery by cesarean section are certain delivery of a living child, with a small but beneficial blood loss to the mother. It is also claimed that by thus removing the supposed source of the toxemia, both maternal and fetal mortality rates would be improved. Unfortunately, none of these advantages accrue, for in the first place eclamptic patients when given a general anesthetic are more prone to develop edema of the lungs, from which they die. Moreover, the tissues do not heal kindly and the risk of infection is greater. As far as the infant death-rate is concerned, little improvement is demonstrated, for the fetus is often premature and is enfeebled by the toxemia which affected the mother; therefore such an infant is equally difficult to raise, no matter how it is delivered.

In discussing the conservative therapeutic procedures for eclampsia seriatim, it is well to emphasize the fact that no one of these measures is universally applicable. Each case must be studied individually. Treatment is directed toward: (1) reducing blood-pressure; (2) increasing the blood volume, thereby diluting the toxin; (3) promoting elimination by every channel; and (4) removing the remote cause, namely, the product of gestation.

To reduce the hypertension venesection and veratrum viride are the most effective means. Under this heading also lumbar puncture would apply.

Venesection.—Venesection phlebotomy, or venepuncture resulting in the withdrawal of from 500 to 700 c.c. of blood from the median basilic vein is the most effective means of accomplishing the first result desired in the treatment. Blood-pressure readings, taken on the other arm, are an index of the amount of blood to be removed. Venesection at once reduces blood-pressure, relieves the circulation of a certain proportion of the specific toxin, and promotes resorption of the edema and fluids which have escaped into the tissues. Clinically, the patient at once becomes relaxed and usually breaks into a brisk perspiration. Cragin claimed that venesection induced considerable shock, but such has not been my experience. There should be little trauma and no shock if the blood is withdrawn slowly through a needle and the procedure controlled by frequent blood-pressure readings. There is one possible risk in bleeding an undelivered patient with eclampsia, namely, that a further loss of blood during the third stage of labor might seriously affect her. I can conceive of a serious hemorrhage as the result of a deep, cervical laceration or from an adherent placenta which, when shortly superimposed upon a venesection, might prove fatal. However, the delivery of a patient under proper surroundings and with adequate technical assistance is not commonly associated with extensive damage to the birth canal. In the second place, these patients rarely experience even the usual blood loss from the uterus during the third stage. I have frequently hoped that a patient whom I was watching under the "expectant" régime might suffer a further blood loss to benefit her general toxemia, but uniformly I have been disappointed.

Veratrum Viride.—This drug actually reduces blood-pressure and was advocated by Cragin and B. C. Hirst to secure the same effect as venesection. They report satisfactory results; but it must be emphasized again that, where routine measures are employed, it is difficult to evaluate each. It appears that Veratrum viride accomplishes its physiologic effect by cardiac depression and by peripheral dilatation, but this result is accomplished only at the expense of the patient, and does not dilute or remove the toxin. Obviously, neither venesection nor Veratrum viride are indicated in those rare cases of eclampsia that manifest no hypertension.

Lumbar Puncture.—After an extensive study of the literature in regard to "edema of the brain" and the value of lumbar puncture, with only ten personal experiences with the procedure, I think it may safely be said that, aside from the risks attendant upon all lumbar punctures, the procedure is rational in eclampsia, but its beneficial results are not proved. I have reserved the procedure in my practice for postpartum eclampsia, in which cases I have never been sure whether it was the lumbar puncture or other routine procedures for combating the disease that have caused the rapid recovery of the patient. Certainly it only removes one manifestation of the disease and not the primary cause.

As a means of diluting the toxin and prompting elimination, fluids must be forced. The most effective channel is water by mouth and, in addition, salt, glucose or bicarbonate of soda solutions through proctoclysis, hypodermoclysis or intravenous injections. Despite the fact that these patients are usually restless and irritable, occasionally unconscious, and always desperately ill, a stomach tube inserted with care usually will not cause a convulsion. Having inserted the stomach tube, the stomach should be washed out and a liter to a liter and a half of tap water allowed to run in slowly. To the last portion of the fluid three drops of croton oil or an ounce of castor oil may be added. The whole procedure, without the purgative, may be repeated every four hours. The greatest advantage is gained in diluting the toxins and breaking the hepatic or renal block, by administering a quantity of fluid and not an attenuated stream. Probably the best method is the physiological channel, the stomach; however, the next best, if not an equally efficient method, is the intravenous injection of isotonic salt solution. Hypodermic injections of salt solution are more slowly absorbed and therefore in an unconscious patient this means is useful as an adjunct to one of the former methods. Those patients do best who, in the intervals between convulsions, are conscious enough to swallow water. Probably the least effective, but nevertheless an additional and fairly serviceable, method is the exhibition of fluid to the patient by proctoclysis.

Glucose Injections.—The slow intravenous injection of 300 to 500 c.c. of a 5 per cent glucose solution has been advocated as a specific remedial measure. I am not prepared to criticize this method of treatment, for it conforms to two of my firm beliefs: (1) that fluid should be injected; and (2) that glucose in the quantity of 1 gm. per kg. body weight is a fair test of hepatic efficiency. I am not prepared to say that this promotes repair of a damaged liver, but it would seem that patients so treated have shown less extensive liver injury.

Bicarbonate of Soda Solution.—I think it is proved that eclampsia is neither an acidosis nor dependent on a defect in protein metabolism. Therefore, the advantage to be derived from injections of soda solution is no greater than that to be derived from similar solutions containing salt. Furthermore, death may follow too free use of an alkali. Soda solution has not the advantage of glucose solution, for the latter is at least high in food value. However, the alkali may have some specific effect upon the excretory ability of the renal epithelium.

No means of stimulating the emunctory organs, of bowel, kidney and skin, equals the ingestion of fluids, but certain drugs may be used as adjuvants, such as croton oil and castor oil for the bowel. Underhill claims that magnesium sulphate as a purgative acts through its hygroscopic quality and merely removes water as fast as it can be ingested. If this is the case, it is doubtful if any considerable amount of toxic substances is eliminated with the resultant fluid stool. Consequently the use of such a purge would defeat the original aim. Diuretic drugs are not effective and the use of pilocarpin for diaphoresis is dangerous and therefore to be condemned. In view of the fact that it is requisite to promote elimination by every channel, considerable strain has been put upon patients in the past by means of hot packs, sweating cabinets and like maneuvers to stimulate perspiration. As a matter of fact, elimination by the sweat glands is limited in effectiveness, and may be induced by keeping the patient wrapped in blankets, warmed by hot-water bottles and guarded from undue exposure.

Under the fourth method of treatment, the removal of the products of conception, various methods of inducing premature labor are to be considered, such as the insertion of bougies or bags and the termination of labor by forceps, or by version and extraction.

Meanwhile the distressing clinical manifestations, the convulsions, must be controlled and the extreme nervous irritability must be alleviated. For this purpose morphia, chloral hydrate, paraldehyd and chloroform have been used. The last-named drug has a destructive effect on the liver similar to that of the disease itself; therefore, the use of chloroform as an anesthetic or to alleviate the convulsions has been abandoned. At the Dublin Rotunda the use of large doses of morphia has proved successful, and it is strongly recommended. The administration of this drug is regulated after the initial dose by the rate of respiration and the frequency and severity of the seizures. Originally, it was recommended that the respiratory rate be reduced to 8 per minute, but this is extreme. All dosage must be based on the weight of the patient and the degree of her response to external stimuli. Obviously such a complete narcotization of the patient is not without risk in unskilled hands. Studdiford is using paraldehyd intravenously in lieu of morphia. While paraldehyd is less toxic than morphia, it is a cardiac depressant and a possible theoretical objection to its use rests on the fact that it may be injudiciously administered to a patient already under a severe physical strain. Chloral hydrate is likewise variable in its effect on individuals, is a depressant and is rather more difficult than either morphia or paraldehyd to control.

Thyroid extract has been recommended for the treatment of eclampsia. Percy says that in the cases in which this drug has not been effective, the dosage has not been adequate, therefore he advises 50 gr. in the first twenty-four hours and 20 gr. daily thereafter. The rationale of such treatment is not clear, and I have no personal experience with the remedy.

It would appear, then, that the so-called "expectant" treatment of eclampsia as first advocated by Strogonoff gives more successful results than the radical operative measures to terminate pregnancy or labor. The use of the several medical measures is governed by two clinical guides: (1) the blood-pressure readings; and (2) the frequency and duration of the convulsions. It is likewise apparent that the conduct of the case along conservative lines occupies a much longer space of time, during which the patient cannot be left alone and most of which time the physician must be in constant attendance. Questions involving the nicest judgment arise without warning. Were it not for the fact that the private practitioner can accomplish a great deal toward its relief when first called to see a case of eclampsia, and that thousands of such cases arise in isolated communities away from adequate institutional facilities, I should at once recommend hospitalization of all toxemias.

After having recited the means at hand for combating eclampsia and the result desired from the employment of each, together with a warning as to the particular attention which must be devoted to the patient during such a course, it must be reiterated that the physician must evaluate each of these maneuvers and drugs one by one and apply them to individual cases under their particular indications.

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DISEASES DUE TO PHYSICAL AGENCIES

CHAPTER XLVII

SEASICKNESS AND CAR (TRAIN) SICKNESS

C. S. Butler

SEASICKNESS

Seasickness is the term applied to a symptom-complex, characterized by nausea, vomiting and giddiness, and induced typically by the motions of a ship at sea.

The cause is not thoroughly understood, but it is most likely the result of several factors operating together, the chief of which is disturbed functioning of the equilibratory apparatus of the internal ear and cerebellum. The symptoms may be readily reproduced by spinning rapidly on one's feet or in a Bárány chair, which is devised for the diagnostics of equilibration, and they may be experienced to a minor degree in a rapidly descending elevator or by swinging in a free-moving rope swing. The psychic element involved may be noted by many people on looking down from a high building.

The capacity to adjust oneself readily to changing positions varies greatly with individuals and is a matter which must be taken into consideration in the selection of aviators. By practice that capacity may be developed to a very high degree as is seen in the professional "whirlers" who may turn the body rapidly for several minutes with no apparent discomfort or disorientation.

To most people the slighter undulatory movements of a ship are pleasurable. The semicircular canals send in the proper warnings, these are properly coördinated and the necessary muscular responses are brought into play to adjust the body to the changing positions of the ship. With the more active movements of the vessel, however, there is a delay in the response from the canals, resulting in a confused coördination, a lack of muscular adjustment and the psychic shock which results from disorientation. These rapidly recurring shocks produce the dizziness, malaise, nausea and vomiting which make up the ensemble of seasickness. Man's normal life being lived on a solid foundation, his equilibratory apparatus is tuned and timed to changes in bodily position over which he has more or less control. On a ship conditions are different and it is necessary that the reflexes for equilibration be accomplished more quickly in order that he may be brought into proper adjustment with his surroundings. In a motor, if the timing apparatus is adjusted so as to fire the gas at the wrong time in the cycle, the full power of the fuel upon the machinery is not obtained. So in seasickness the reflexes are timed too late and control of the body's position is imperfect and confused.

There is little possibility that any drug will ever be found, or any mechanical appliance devised, for steadying ships, which will completely prevent seasickness. From what has gone before it will be inferred that all drugs can do is to deaden the nervous system to the results of its own shortcomings. As regards the steadying effect of mechanical devices upon the ship itself, we may venture to predict that none will ever be perfected which will prevent the vessel's pitching, which is by all odds the motion most effective in producing the symptoms.

Every individual has a "symptom threshold" for seasickness, that is, a point in relation to the motions or combination of motions of a vessel beyond which he cannot go without manifesting some subjective or objective evidence of distress. The old sea dog has "no stomach" for his smoke perhaps in heavy weather, or the well-traveled young lady, who has made so and so many trips "across" and never been seasick, may acknowledge to herself that there is an unusual amount of saliva secreted, and that the recumbent position is desirable. This threshold is variable and stands in direct relation to the individual's general well-being. It may be elevated by good personal hygiene or depressed by bad. For this reason aviators are kept under constant medical supervision and if not in perfect physical tune are not allowed to go up. If below par the lowered oxygen tension of high altitudes may lower their threshhold so that air sickness—the counterpart of seasickness—results.

Neptune is a great joker. He makes the average citizen want to die of this awful complaint (seasickness) and then after a few days his former willing victim may gaze complacently from the poop or the bow at his ground and lofty tumbling and declare him a pretty good fellow after all. Seasickness practically never kills any one; generally speaking, it is good for diseased conditions, though it may stir up an old appendix or give gall-stones an attack of the Wanderlust. It may start hemorrhage from or cause perforation of a duodenal ulcer.

What has happened to the man who on the first day out on a voyage was the picture of impending dissolution, both mental and physical, and yet who on the sixth day can shake his fist at the sea and say "to-morrow do thy worst for I have had to-day?" Evidently some wonderful change has been brought about in this man and in our opinion that change consists in a better timing of those nervous impulses which have to do with the reflexes for coördination. This opinion is based upon the following facts: (1) animals whose semicircular canals have been obliterated do not get seasick; (2) deaf mutes, whose semicircular canals are poorly developed, do not suffer from it; and (3) the symptoms of seasickness may be reproduced by rapid rotation of the body, which fact we may best explain as due to imperfect registration of the pressures of endolymph in the semicircular canals. J. R. Stocker, writing on seasickness in Albutt's System, enumerates twelve theories as to the causation of this condition. Doubtless each of these twelve has some influence in making the victim more miserable after symptoms start, but in our opinion the first and chief cause is that given above.

The change then which has been brought about in a person who has "found his sea legs" meets its best explanation in Ewald's suggestion as to the function of the impulses from the semicircular canals, namely, that the stream of impulses having their origin there initiate the constant state of reflex activity on which depends the tonus of the body musculature, visceral as well as skeletal. This tonus, according to Howell, "may vary in an adaptive way in different muscles according to the strength of the stimuli coming from one or another of the canals." Evidently, if these impulses are imperfectly assembled and registered the tonus will be imperfect and faulty. All the musculature of the body, voluntary and involuntary, seems to share in the faulty performance which occurs in the seasick man, and when this man has educated his semicircular canals to make the proper returns at the proper time the reflexes essential to proper tonicity return and he has "found himself" on the ship, to go with her where she goes and not resist, to be a part of her structure, so to speak, rather than an inanimate mass of protoplasm to be jostled at the caprice of the sea.

If we have seemed to belabor the argument of this point, it has been in order to outline a rational course for the prevention and cure of a very distressing complaint, and to show the utter futility of drugging the vast majority of those who from choice or necessity go down to the sea in ships. Fully 95 per cent of people may by proper hygiene and precautions come to qualify as good sailors, that is, may learn to be comfortable and to be able to "carry on" under the *ordinary* weather conditions which prevail on the ocean. To prepare a candidate for a degree in Neptune's School by administering bromids before starting on a voyage is about as logical as trying to learn Greek by reading an English translation of Homer. The passenger (let us say, a female passenger) under these circumstances goes on board not knowing what her threshold is, but she may rest assured that it is lower than if she had *not* taken the bromids. Let us say that this passenger after departure gets seasick. She is physically sound but, noting the weakness of her pulse, and coldness of her extremities, we "try" digitalin. Pretty soon, in addition to her other miseries we have conferred an artificial heart block upon her. When the ship reaches its destination seven days later this lady is carried ashore on a stretcher, and doesn't get over the effect of her doctors for a week. Neptune is blamed when it should be Æsculapius. Thus we find that most of the drugs in the pharmacopeia have been declared "specifics" in seasickness. If the patient can stand alone and walk down the gangplank at the other end of the voyage, the drug is a "specific"; if she has to be carried off, the drug has failed.

The preparation of the prospective voyager should take the direction then not of lowering the capacity of the cells and organs of the body to perform their function, but rather of bringing each and every one of them to the highest point of functional capacity. Every physician whose duties connect him with ships and ocean passenger traffic should read the excellent article by Professor C. M. Belli of the Royal Italian Navy on "Personal Hygiene of Aviators." While the paper is written for people who go up in airships, it applies in almost every detail to passengers on ocean-going vessels.

Every one whose profession or whose pleasure takes him to sea should have an ambition to become a good sailor. Just as it is desirable and healthful for every one to learn how to swim, so it is desirable and healthful for every one to learn the knack of being a good sailor. The acquisition of this accomplishment is, like learning to swim, oftentimes quite an ordeal, but it is neither logical nor good therapy to depress ourselves with alcohol or morphin or bromids when we are preparing for the swimming ordeal. The same applies to the sailoring ordeal. A clear head, a clean gastro-intestinal tract and a few words of encouragement and advice are the items the prospective passenger should get from the physician. Moderation in all things as a habit of life, but, if not that, then for at least a week before sailing will accomplish the first item. This clearness of head will be helped by the accomplishment of the second item, namely, the cleansing of the gastro-intestinal tract, and the keeping of it in active functioning condition until and after the candidate has found his sea legs. To this end, a mild laxative should be taken each evening at bedtime for about a week before sailing. An ideal combination for this purpose is the pill containing aloin ⅕ gr. (13 mg.); extract of belladonna, ⅛ gr. (8 mg.); strychnin, the pure alkaloid, 1/20 gr. (3 mg.); and ipecac, ⅙ gr. (11 mg.) in each pill. Most of the pharmaceutical companies put up combinations of this composition, and they are excellent. A bottle of these pills should be carried in one's handbag, and one taken each night on retiring when there is any tendency to costiveness. The small amount of ipecac in this pill is not nauseant in its effect but stimulant, and aids the other constituents, two of which (the strychnin and belladonna) figure in many of the specifics for seasickness. Phenolphthalein, or phenolphthalein-agar, or the salines, or a course of calomel and soda followed by a seidlitz powder, any of these may be used to advantage. The first-mentioned pill, however, we have found so satisfactory and so easily transportable that we prefer it. Whatever laxative is used, the passenger should take a colonic irrigation shortly before embarkation, and should go on board hungry. Every passenger, who has not made a previous voyage and who, therefore, doesn't known what his "vestibular performance" will be, should provide himself, in addition to the bottle of pills, with a soft rubber bulbed syringe for taking an enema. He should not pass any day without a free movement of the bowels even if resort must be had to the enema. He should let nothing interfere with regular habits of going to the toilet, bathing, and the proper care of the teeth, nostrils, and eyes.

Passengers are not long in learning that the place of least motion is amidships, that the recumbent position is (for squeamishness) the most comfortable, that the open air of the deck is much better than the stateroom, and that, on the weather side, he avoids disagreeable odors. Each of these should be taken advantage of if one is at all uncomfortable. The tendency to recline in one's stateroom should be discouraged, and all of the open-air exercise (games, etc.) that one can take will be found to be a help towards forgetting about the ship's movements. If the nausea is too great, it will be found a great relief to drink a glass or two of tepid water, tickle the pharynx with the index finger, and wash the stomach out in this way. When much mucus and saliva have been swallowed, this simple procedure will enable the patient to take a new hold on life. It is oftentimes successful, too, when there has been considerable vomiting which is kept going by bile regurgitated into the stomach.

After this washing out of the stomach, if the patient will lie down for a time in a quiet part of the ship and then take some hot broth or a little tea and toast, it will be found that from this moment he will begin to recover from his incapacity to walk around, and enjoy life. It would seem to be a mistake to crowd the food as a weighted stomach jostles more than an empty one, and who knows but that the vomiting is nature's effort to throw off all handicaps to a sorely embarrassed nervous system? There is no danger of the patient's dying of starvation, for, even on the longest voyages, it is seldom that a run longer than ten days is made without a respite. The condition is usually recovered from within five to six days, and, once recovered from, seasickness doesn't trouble the individual again except under unusual stress of weather or bodily depression.

In prolonged seasickness, the physician should always satisfy himself that there is no mistake in the diagnosis. Complications should be watched for. Appendicitis, cholecystitis, gall-stone attacks, kidney-stone attacks, pneumonias, etc., are proportionately as common on the sea as on shore. Fever and leukocytosis are not symptoms of seasickness and their presence should always put the medical attendant on his guard. It is the part of wisdom before going on a sea voyage to undergo a thorough medical overhauling, and if any remediable surgical condition exists, which might be lighted up by seasickness, it should be attended to before making the voyage. Except in conditions such as those just mentioned, seasickness seems to do no damage. Sea voyages are not contra-indicated in diseases of the heart, kidneys, or blood-vessels.

As has been said previously, the death-rate from seasickness is nil. The following table shows the number of cases admitted to the sick list and the rate per thousand for the years 1917 to 1921, inclusive, in the U. S. Navy.

Case Incidence and Annual Rates per 1,000 for Nausea Marina in the U. S. Navy, 1917-1921

Year	Number of Cases	Annual Rate per 1,000
1917	91	.37
1918	509	1.01
1919	352	1.18
1920	30	.21
1921	44	.30

It will be seen from this how insignificant is the damage among a class of men who make a business of going to sea.

Rarely does a man have to be surveyed from the Naval Service on account of chronic seasickness, and these cases are generally open to the suspicion of malingering.

For the extremely rare individual who is deathly sick all the while at sea, the only thing to do is to treat the nausea along general lines and advise against sea voyages except when absolutely necessary. Of the sedatives, cocain, morphin, or the bromids in the order mentioned are best. The general principles laid down above combined with careful dieting apply also to these rare cases.

Professor Robin's formula for use in vomiting may be tried in these extreme cases. It consists of picrotoxin, 1 gr. (50 mg.) with enough alcohol to dissolve it; atropin sulphate, 1/6 gr. (10 mg.); extract of ergot (purified) (Bonjean's ergotin) 15 gr. (1 gm.); and 3 drams (12 gm.) of cherry laurel water; 5 drops to be taken in a little water ten minutes before the meal.

E. A. Lemon has found that packing both external auditory canals tightly with gauze so as to cause a sense of pressure against the drums will relieve seasickness. That this was the reason for alleviation of symptoms in his cases is shown by the fact that removal of the gauze caused a return of symptoms.

P. Cazamian explains the hypertension which he finds exists in the early stage of seasickness by overproduction of epinephrin, and the lowered blood-pressure of the latter stage to its exhaustion. He would, therefore, give atropin sulphate in doses ranging from 1/60 to 1/30 gr. (1 to 2 mg.) hypodermically in the hyperepinephrin stage of the complaint, and, in the second stage, epinephrin by mouth, 1/10 gr. (6 mg.) in three doses at half-hour intervals.

Lewis Fisher, in an excellent article on seasickness, offers some good suggestions as to prevention and cure. One of these is that those who contemplate making voyage have their vestibular threshold appraised. This could be done in the general medical overhauling spoken of above. Fisher's further suggestion that the Bárány chair be utilized to bring up one's threshold is not so appealing. It would seem best to allow the ship to initiate and complete the immunizing process. When the immunity begins to come the victim gets the mental pick-up which a disappointed suitor experiences when his girl tells him that bygones will be allowed to be bygones, and reinstates him. One cannot gain an affection for "all that dolphined deep where the ships swing" by turning violently in a revolving chair. The nausea thus produced has none of the compensatory advantages which one gets from the sea.

CAR (TRAIN) SICKNESS

There can be no doubt that the method of production of car sickness is identical with that of seasickness, that is to say, its origin is vestibular. The symptoms are similar, but less in degree than is the case with seasickness. Dizziness, malaise, pallor, headache, constipation and at times vomiting make up the picture. Crooked railroad beds and poor engine drivers make for increased incidence of car sickness. The reclining position, facing the head of the train and good ventilation of the compartment tend to lessen it. As regards its prevention and cure, the procedures outlined under seasickness apply here. A freely acting colon which is kept acting by mild laxatives while on the journey, analgesics and smelling salts to allay the headaches and a limited but appealing diet are the indications. Much discomfort can be avoided on going aboard of a train by a formal orientation of oneself. It is often the case that a car-sick passenger doesn't realize which is the head and which the rear of the train nor whether he is riding backwards or forwards. A thorough orientation of oneself immediately upon going aboard of a train and a size-up of the general direction in which the train is moving will do much to prevent car sickness. For long journeys on trains, one's habits are much interfered with. Cramped sleeping quarters make for imperfect sleep; lack of a general morning bath, limited toilet facilities, cramped eating quarters, all tend to make one feel below par. Extra effort should, therefore, be made to carry out one's daily routine as fully as is compatible with the limited facilities available. The laxative pill spoken of under seasickness will be found a useful companion for those who make long train journeys and are inclined to costiveness.

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CHAPTER XLVIII

THE TREATMENT OF MOUNTAIN SICKNESS

Yandell Henderson

Mountain sickness is a form of prolonged partial asphyxia, in the sense of oxygen deficiency without excess, but rather with deficiency also, of carbon dioxid. It is thus closely similar in its etiology to the effects of carbon monoxid asphyxia. From the standpoint of therapy this similarity is noteworthy, for the most effective treatment of the latter condition has recently been shown by Henderson and Haggard to consist of inhalation of oxygen (94 or 95 per cent) with enough carbon dioxid (about 5 per cent) to stimulate the breathing, which becomes depressed in profound asphyxia.

The mass of oxygen in unit volume of air (a liter) decreases as we ascend from sea level, where the barometer is 760 mm. of mercury. The pressure of the atmosphere falls about 25 mm. for each thousand feet of altitude up to 10,000 feet, and somewhat less rapidly at higher levels. The percentage composition of the air is constant at all altitudes, with nearly 21 per cent of oxygen everywhere. Thus the mass of oxygen in unit volume, such, for example, as a breath of a volume of 500 c.c., varies in amount directly with the barometer.

This decreased mass of oxygen in each breath at great altitudes is in part compensated by the greater depth, and on exertion the greater frequency also, in the breathing of persons acclimatized to altitude. There is also a slowly developing increase in the number of red corpuscles. Mountain sickness usually occurs, however, in persons in whom these compensations have not, or not fully, developed.

The disorder varies greatly in degree in different persons, and varies also according to the suddenness and duration of exposure to low oxygen. Thus balloonists and aviators in very rapid and lofty ascents exhibit symptoms of simple asphyxia, including muscular incoördination, disturbance of judgment, perverseness of temper of an alcoholic character, complete failure in most cases to appreciate their own condition, and finally unconsciousness, sometimes with convulsions if muscular work is attempted. In extreme cases death occurs, particularly in balloonists.

Men of otherwise equal vigor vary enormously in their resistance to low oxygen, some collapsing at 10,000 feet, others only at or above 19,000 or 20,000 feet. In some cases, consciousness fails before the circulation, and the individual continues to sit stiffly upright, immobile and unconscious; in others syncope occurs first and the person collapses on the floor.

Persons who ascend mountains on foot, and so have time for some degree of acclimatization to develop, show a picture very much like that of seasickness, but with much more intense headache, which is usually frontal. These effects are not, however, the immediate effect of the low oxygen at the moment, for it frequently happens that they develop most acutely some hours after the summit has been reached, while in other cases the illness develops several hours after return to low levels. In all cases, however, the deficiency of oxygen is the fundamental initial cause of the condition. The headache is probably due to edema of the brain.

A third condition which has now become important is the air staleness of aviators. It results from ascents day after day for a few hours each. No acclimatization is thus acquired. But on the contrary a condition essentially like the overtraining of an athlete develops. Rest and cessation of flying are generally sufficient as treatment. Neurasthenia and cardiovascular weakness in such cases may be handled along general lines.

The *prophylaxis* of mountain sickness consists in a very gradual ascent, taking days or weeks to attain an altitude of 10,000 feet, and only increasing the altitude above this level even more slowly. Strong men may thus without appreciable mountain sickness develop an acclimatization enabling them to perform the work of climbing, although necessarily slowly if the oxygen supply is not to be exceeded and collapse induced, at more than 20,000 feet. Persons with cardiac disorders or obesity should be exposed to altitudes over 6,000 feet only very slowly and cautiously, and should rigidly avoid any exertion.

The more acute symptoms of mountain sickness can be treated only by bringing the patient to a lower level or by administering oxygen. For the latter purpose the gas must be administered either by means of a well-fitting mask or through a tube, the end of which the patient holds in his mouth. Alcohol even in small amounts exacerbates the symptoms of mountain sickness, and may induce them in persons who otherwise would escape. Absolute rest in a recumbent position and transportation for those acutely affected are highly advisable. Otherwise damage to the heart is liable to occur. A sudden chill sometimes produces fainting in those who had not felt badly before, and the patient should therefore be kept comfortably warm. Hypertonic saline intravenously, or even a saline cathartic, may relieve the headache.

Pneumonia is the greatest danger for residents and visitors at great altitudes, and is almost always quickly fatal unless the patient is immediately transported to a lower level. Oxygen therapy would probably accomplish the same benefit, but for this purpose a special chamber, or the continual use of an inhalator with close-fitting mask is necessary. The administration of oxygen as usually practiced, by discharging the gas from a funnel near the patient's face, is too inefficient to be of any appreciable value at an altitude, or indeed even at sea level.

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